Review Article

Distress, Depression, Anxiety and Cardiovascular Disease: A Call to Action

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ABSTRACT

Research surrounding the relationship between depression, anxiety, and cardiovascular disease (CVD) is rich and rapidly evolving. This research article shows that depression, anxiety, and subsyndromal symptoms of these disorders known as *distress* (i.e., chronic anger, worry, hopelessness) are significant independent risk factors for CVD both etiologically and prognostically – as significant as smoking. On this basis the American Heart Association listed depression as a major independent risk factor for heart disease in February of 2014 and strengthened its guidelines for the screening and treatment of depression in people with heart disease.

Most heart patients will suffer from depression, anxiety, or both at some point along the etiological continuum, and effective treatment of these problems has been shown to improve cardiac outcomes, yet evidence-based treatment for depression and anxiety remains elusive for the vast majority of cardiac patients. Diagnostically, the screening instruments in use have proven adequate but treatment-wise, intervention has been reduced to prescribing SSRI medications. However, SSRI's show clinical effect less than half the time, have recently been shown to be no better than placebo, and have mild cardio-toxic effects. Psychotherapy and clinical hypnosis have proven effective but can take too long, can be costly, and are difficult to provide in cases where properly trained doctoral-level clinicians are lacking. Meditation has been proven effective in the treatment of coronary artery disease (CAD) and for mild to moderate depression and anxiety but most cardiac patients quit its practice before it can deliver clinical benefit, and it is not effective as a stand-alone intervention for moderate to major depression and anxiety.

The author, having recently published a patient self-help manual on this topic, calls for emphasis on developing innovative new methods for the treatment of depression, anxiety, and subsyndrome distress for cardiac patients that are effective, rapid, and reasonable in cost. Further, owing to the epidemic rise of chronic stress, depression, and anxiety in India (the WHO estimates that 35.9% of India's populace will experience depression at some point in their lifetime; approximately 1 in every 5 urban residents currently suffers from anxiety), the author suggests that cardiology should take the lead in promoting effective, innovative primary prevention programs aimed at reducing stress, depression, and anxiety in the general population if we are to prevail against CVD in India. (J Clin Prev Cardiol 2014;3(4):107-40)

Rising Incidence Rates of CVD in India

By the year 2020 heart disease is projected to be the number one cause of death worldwide and a particular challenge for India (1). According to WHO statistics India has the highest rate of CHD among developing nations and experiences more than twice the rate of death per 100,000 population due to CHD as the United States (2). A review of data from the Registrar General of India by R. Gupta showed that CHD is responsible for 40% of urban deaths, 30% of deaths in rural areas, and growing at a phenomenal rate, increasing in urban areas from 1960 to 2000 by more than 500%, and in rural areas from 1970 to 2000 by nearly 250% (3). A related study by R. Gupta *et al*. found that tobacco use, obesity with a high waist–hip ratio, high blood pressure, high LDL-C, low HDL-C, abnormal apolipoprotein A-1:B ratio, diabetes, low consumption of fruits and vegetables, sedentary lifestyles, and psychosocial stress are important risk factors for CHD in India (4).

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Depression and Heart Disease

More than 60 prospective studies, over 100 narrative reviews, and numerous meta-analyses firmly establish clinical depression and subsyndromal depressive symptomology (i.e., hopelessness, sadness) as major independent risk factors in the etiology of heart disease and cardiovascular morbidity and mortality.

A review of 13 large, prospective, longitudinal studies by Duke University Medical School concluded that depressive disorders, as well as subclinical depressive

symptoms like "hopelessness," correlate with an almost three times higher risk of developing coronary artery disease (CAD). Depression and depressive symptoms are also associated with 2–3 times higher mortality rates for patients with stable CAD and for those who suffer myocardial infarction (MI), unstable angina, and coronary artery bypass. Remarkably, these correlations held after adjustment for conventional prognostic risk factors like smoking, hypertension, and obesity (5).In one of the earliest longitudinal studies ever conducted, all male medical students who entered The Johns Hopkins Medical School from 1948 to 1964 were followed annually until the study results were reported in 1998 (6). Respondent-reported data were verified against medical records by a committee of physicians. The definition of CAD included MI, angina pectoris, chronic heart disease, and other types of symptomatic disease that required coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. The cumulative incidence of clinical depression in this cohort of 1,190 participants at 40 years of follow up was 12% (lower than the incidence of depression in the general population). In this study, clinical depression was associated with a more than twofold higher risk of later CAD. Significantly, this correlation did *not* change after adjustment for body mass index (BMI), premature parental heart attack, cholesterol level, smoking, hyperlipidemia, hypertension, and diabetes mellitus. The median time from the first episode of depression to the first CAD event was 15 years.

Penninx *et al*. followed a large cohort of both men and women aged 55–85 years for 4 years, and found that subjects with no history of heart disease at baseline who met DSM-III criteria for major depression experienced a 3.9-times higher risk of heart-related mortality compared to those with no sign of depression (7). In another study, Pratt *et al*. used a structured interview to assess the incidence of major depression among study participants using DSM-III criteria (8). In this study, patients with major depression had a 4.5-times higher risk of experiencing a heart attack (MI) during a 13-year follow up than those without major depressive disorder (MDD). Patients with depressive symptoms that fell below the clinical criteria for major depression were twice as likely to die of MI as patients with no depressive symptoms whatsoever. Other longitudinal studies confirm that subclinical symptoms such as "hopelessness" and "a tendency to worry" are associated with a higher incidence of angina, MI, and death (9–11). Glassman *et al*. showed that depression's effect on increased rates of morbidity and mortality for patients with CAD is independent of conventional risk factors such as high blood pressure, obesity, smoking, or high cholesterol (12).

Studies that focus on women and heart disease are of particular interest because research in both the US (13) and Europe (14) confirms that mortality rates in women patients exceed those in men, even after taking age and comorbidities into account.

Prevalence rates for depression among women are higher than rates for men both in the general population (15), and among cardiac patients (16). In one of the earliest studies focusing on women, Hallstrom *et al*. conducted comprehensive medical and psychiatric examinations on a large sample of women in Gothenburg Sweden (aged 38–54 years) between 1968 and 1969, and then followed them for 12 years for occurrence of angina pectoris, MI, and death (17). Depressive symptoms were scaled from 0 to 4, with a grade of 2 or higher equivalent to clinical depression. In this study, the higher the depression grade, the greater the incidence of morbidity and mortality due to heart-related pathology. A high depression grade correlated with an almost threefold increase in risk for angina pectoris. Subclinical, fairly common depressive features like feelings of guilt and low self-assertiveness were also associated with an increased risk of MI.

In sum, the correlation between depression and cardiovascular problems appears to be comparable to the correlation between smoking and CVD (18). As with smoking, there is a dose–response relationship between depression and CVD: a few symptoms of depression may double a person's risk of developing CVD and experiencing a poor prognosis, whereas patients who meet the diagnostic criteria for major depression are many times more likely to develop heart problems and experience higher rates of morbidity and mortality postdiagnosis.

These longitudinal studies indicate that depression most frequently occurs before the onset of clinically significant CAD. Clearly, a diagnosis of CVD, the physical degradations and disabilities associated with it, and the stress of medical procedures and surgery, are

significant enough to cause or exacerbate depression in people with heart disease.

A range of studies have found high rates of clinically meaningful depressive symptoms among cardiac patients. One authoritative study by Denollet and Brutsaert placed the incidence rate of clinical depression among cardiac patients as high as 50.5% (19). Schleifer *et al*. reported that among 171 hospitalized MI patients, 45% met criteria for major or minor depression (based on research diagnostic criteria) 8–10 days after MI, and 33% met these criteria 3–4 months later (20).

Anxiety and comorbid depression and anxiety are more prevalent than depression post-MI, but a range of studies have reported rates of clinical depression approaching 45% in patients who have suffered MI, with 19–23% of all post-MI patients meeting the criteria for MDDs (21–23).[

When we look prognostically at the risks associated with higher morbidity and mortality for patients with a diagnosis of CVD and depression, we see the mortality rate among clinically depressed patients is quite high and increases with the severity of symptoms and passage of time. The relative risk ratio for death within 6 months among post-MI patients with MDD, versus post-MI patients without depressive disorder, was reported as 3.1 by both Schleifer *at al.* (24) and Frasure-Smith *et al*. (25). In a study by Lesperance *at al*. (26) 430 patients who were hospitalized for unstable angina without the need for coronary artery bypass surgery were followed. Patients with MDD (a score of 10 or more on the Beck Depression Inventory [BDI]) had a rate of death due to MI at 1-year follow up that was almost five times higher than patients without depression – a risk ratio that remained after controlling for baseline electrocardiographic evidence of ischemia, left ventricular ejection fraction, and number of diseased coronary arteries. A different study by Frasure–Smith *et al*. found that patients with MDD were almost 7 times more likely to die in the 18 months following MI than patients whose BDI score was less than 10 (mild to moderate depression). This risk was independent of other known risk factors for mortality in this population, including previous MI and frequency of premature ventricular arrhythmia (27). Of patients with known CAD but no MI, a number of studies show that anywhere from 12% to 23% have MDD according to DSM-III or DSM-IV criteria, measured using standardized structured interviewing (28–31).[[2] In one well-controlled study by Carney *et al.* (32) a diagnosis of major depression was the best predictor of cardiac events for this population (MI, bypass surgery, or death) at 1 year, better in risk prognosis than impaired left ventricular function, severity of CAD, and smoking. The relative risk of a cardiac event for depressed patients in this study was 2.2 times higher than for nondepressed patients.

A review of 11 rigorous studies examining this relationship conducted by Jiang *et al*. showed that patients with depressive disorders are 2.3–7.5 times more likely to die within 1 year post-MI than the patients without depressive disorders (33). The wide range of risk across studies is associated with different scales used to measure depression and subsyndrome depressive symptoms, great variation in study length, and substantial difference in study cohort characteristics (age, gender, socioeconomic status, diagnosis). Generally: (i) the more severe the depression, the greater the risk of morbidity and death; (ii) younger age at onset of depressive symptoms results in more severe CVD-related mortality and morbidity; (iii) women with depression are more severely affected over time than men; and (iv) patients who face ongoing sources of psychosocial stress (i.e., conflict with or alienation from their spouses, lack of social support) do poorly compared to patients with intact psychosocial support systems.

In a large study undertaken by Barefoot *et al.* (34)[, 1,250 patients who had undergone their first angiogram were followed long term for a mean of 19.4 years. The incidence and severity of depression were evaluated according to the Zung Self-Rating Depression Scale (SDS). According to this study, the higher the SDS score, the higher the risk of cardiac death and all-cause mortality. Patients who were moderately to severely depressed had a 69% higher risk of cardiac death and 78% higher risk of all-cause mortality when compared to patients without depression. Patients who were mildly depressed had a 38% higher risk of cardiac death and a 57% higher risk of all-cause mortality when compared with nondepressed patients.

A very recent large-scale study conducted by Shah *et al*. (35) examined 3,237 patients undergoing coronary angiography for evaluation of CAD and followed them for a median of 2.9 years with the objective of assessing

whether depression in young women is associated with higher risk of CAD and adverse outcome when compared with similarly aged men and older women. This study found that, after multivariate adjustment for traditional CAD risk factors, depressive symptoms predicted CAD severity and increased risk of death in women 55 and younger, but not in men 55 or younger, nor in women over the age of 55. The authors conclude that younger women may be especially vulnerable to the adverse cardiovascular effects of depression (35).

Studies by Saur *et al*. (36) and Baker *et al.* (37) showed that elevated depressive symptoms before bypass surgery predict increased length of stay after the procedure, higher re-admission rates, and higher rates of both short-term (6 weeks) and long-term mortality. Grenon *et al*. followed 1,024 men and women with CAD for a mean of 7.2 years and found that patients with depressive symptoms were twice as likely as non-depressed patients to develop peripheral arterial disease (PAD) even after controlling for comorbidities, medications, traditional PAD risk factors, inflammation, and health behaviors (38).

Jiang *et al*. (39)[conducted a prospective cohort study to examine whether depression adversely affects prognosis in patients with CHF as it does in patients with CAD and whether such effects occur independent of traditional risk factors. They found that CHF patients who met DSM-IV criteria for major depression had a mortality rate more than twice that of those who were not depressed, and three times as many hospitalizations. They also found the relationship between depression and higher rates of mortality and re-hospitalization was independent of advanced age and severity of ischemic etiology of CHF. These findings are substantiated in studies by Murberg *et al*. (40) and Vaccarino *et al*. (41). In the study by Vaccarino, depressive symptoms of 391 patients 50 years old or older who were hospitalized with CHF were measured, and all patients were followed for 6 months with a focus on mortality and functional capacity (activities of daily living [ADL]). In this study, mortality at 6 months was two to three times higher in patients with greater depressive symptoms compared to patients with lesser symptoms or patients considered to have normal mood. Patients with moderate depressive symptoms also experienced significant functional declines during follow up.

In another well-controlled study by Jiang *et al*., 374 patients, men and women aged 18 or older with New York Heart Association class II or greater CHF, an ejection fraction of 35% or less, or both, were assessed for depression, mortality, and re-hospitalization rates at 3 months and 1 year after depression assessment (42). Of 374 patients screened, 35.3% had a Beck Depression Inventory score of 10 or higher and 13.9% had MDD. Major depression was associated with a 2.5-fold increase in mortality at 3 months relative to nondepressed patients, a 2.2-fold increase in mortality at 1 year, a 1.9-fold increase in hospital re-admission at 3 months and a more than 3-fold increase in re-admission at 1 year, relative to non-depressed patients. These risk ratios were independent of age, New York Heart Association class, baseline ejection fraction, and ischemic etiology of CHF.

In the Myocardial Ischemia Intervention Trial, patients with CHF who had more depressive symptoms showed more ischemia during mental stress testing (43) and feeling "sad, tense or out-of-control" was associated with the incidence of transient myocardial ischemia, as measured by 48-hour ambulatory electrocardiography during daily living.

A recent study designed to assess the impact of changes in symptoms of depression for heart failure patients found that worsening symptoms of depression were associated with higher rates of cardiac death and cardiovascular hospitalization, even after controlling for baseline depression and established risk factors like HF cause, age, ejection fraction, plasma N-terminal pro-B-type natriuretic peptide level, and prior hospitalizations (44). It is well-established that depression is associated with higher rates of healthcare utilization and costs for all heart patients (45).

Biological mechanisms fueling the relationship between depression, subsyndrome depressive symptoms, and heart disease

Studies show that there are several depression-driven biological factors that promote increased morbidity and mortality for people with heart disease (46). Depression and its subsyndrome characteristics of distress are well known to increase activation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in high levels of cortisol and sustained arousal of the sympathetic nervous system (SNS). High levels of cortisol are known to redistribute body fat and increase the risk of heart

disease (47). Intra-abdominal fat, a known risk factor for CAD, has been shown to be twice as high in depressed women as in nondepressed women (48). A number of studies have shown that depressed patients have elevated plasma norepinephrine levels, increased heart rates, and reduced heart-rate variability, all of which are associated with increased morbidity and mortality in CAD and CHF (49–54).[555]

Depression also causes increased platelet aggregation (55) and higher platelet monoamine oxidase (MAO) activity, especially in women (56). Laghrissi-Thode *et al*. found that patients with ischemic heart disease who were also depressed showed elevated β-thromboglobulin levels, increased plasma levels of platelet factor 4, and increased expression of the platelet surface receptors for glycoprotein IIb/IIIa and P-selectin, when compared with nondepressed patients (57). Although smoking and ventricular arrhythmias are more common in depressed patients, depression adversely affects the course of heart disease independent of these factors (58).

Research has substantiated the role that chronic stress and depression play in pro-inflammatory processes. Depression is associated with alterations in immunological functioning relevant to pro-inflammatory processes. Specifically, depression has been associated with an elevation of interleukin-6 (IL-6), a primary pro-inflammatory cytokine (59,60).

Anxiety and Heart Disease

Anxiety's association with CVD has been less well studied than the effect of depression for this population, though the research base is substantial and growing, to such a degree that many researchers in the US have called on the American Heart Association to list anxiety as a major independent risk factor for heart disease.

Anxiety is a negative affective state resulting from an individual's perception of threat, characterized by a perceived inability to predict, control, or gain preferred results in given situations (61). There are several different subtypes of anxiety, including panic disorder, social anxiety disorder, generalized anxiety disorder (GAD), simple phobia, obsessive-compulsive disorder, and post-traumatic stress disorder. Anxiety disorders can evolve as a normal reaction to chronic stress and cumulative adversity, and acutely stressful situations (like having an MI) can trigger anxiety. Anxiety exists along a continuum from normal to pathological. Research strongly suggests that anxiety at every step along the continuum has comparable cognitive, neurobiological, and behavioral effects, and that clinical and subclinical anxiety are not fundamentally different phenomena – both have dilatory effects on patient health (62).

Several longitudinal studies have shown that anxiety is predictive of new onset of CHD. Studies among initially healthy individuals who were followed to detect the occurrence of CHD report a range of prognostic risk factors based on the population under study, outcomes measured, and duration of follow up. Weissman followed 3,778 healthy men and women for the incidence of acute MI and found the probability of AMI in anxious people was 4.5 times as high as risk of AMI in nonanxious individuals (63). In a similar study of 2,280 community dwelling men with a 32-year follow up, the rate of sudden death due to heart disease was 4.46 times higher for anxious individuals than for those without anxiety. A study by Eaker *et al*. of 749 community-dwelling women with 20 years follow-up found the risk of AMI or cardiac death was 7.8 times higher for women with anxiety than for nonanxious women (64). In all these studies, the relationship between anxiety and poor cardiac outcomes was independent of traditional cardiovascular risk factors and there was evidence of a dose–response effect whereby higher levels of anxiety correlated with poorer cardiac health outcomes. In the Women's Health Initiative Study, a 6-month history of panic was associated with 3–4-fold increase in risk of CHD or stroke (65).

Subclinical anxiety also has implications for heart disease etiology. The Normative Aging Study, a large prospective study conducted in Boston, found that higher levels of worry (a key symptom of anxiety) were found to predict increased risks of both MI and fatal CHD in male subjects at 20-year follow up (66). Men reporting the highest levels of worry had adjusted relative risks of MI more than double that of men with the lowest levels of worry. Kawachi *et al*., in a study of 33,999 male health professionals over a 2-year period, found that the risk of CHD mortality was 2.45 times higher in men with some symptoms of anxiety than in those with normal mood (67).Anxiety is also a prognostic risk factor for patients who have already been diagnosed with heart disease. Anxiety is very common among individuals with chronic CHD and individuals recovering from acute cardiac

events – more common than depression. Anxiety has been found in approximately 70–80% of patients who have suffered MI, and it persists chronically in 20–25% of people with CHD who have never suffered an acute event (68).

A number of studies have shown that anxiety predicts a higher incidence of cardiac events, higher morbidity and mortality, and poorer quality of life for CHD patients in both the short and long term, independent of conventional risk factors and disease severity (69–71). Persistent anxiety predicts worse disability, more physical symptoms, and poorer functional status in CHD patients (72,73). It hinders patient self-care abilities post MI (74,75),[7 retards patient ability to implement needed lifestyle changes (76)[, and lowers adherence to physician-ordered rehabilitation efforts (77). Patients with sustained anxiety are more likely to suffer "cardiac invalidism," an old term that describes CHD patients whose level of debilitation after a CHD diagnosis or acute event is unexplained by the severity of their physical condition (78).

Anxiety has been shown to predict future coronary events and long-term survival after MI, even after controlling for disease severity and conventional risk factors (79–81). Anxiety post MI is also associated with increased in-hospital complications such as lethal dysrhythmias, continued ischemia, and reinfarction (82), longer stays in the cardiac care unit and hospital (83)[, more frequent and severe symptoms, regardless of the severity of a patient's physical condition (84), higher consumption of healthcare resources, and lower quality of life post-discharge (85).

A very large prospective, comparative, cross-cultural investigation by Moser and De Jong was designed to evaluate the impact of anxiety on patient health soon after MI in five countries: Australia, England, Japan, South Korea, and the US (86). This study found that individuals from different ethnic and cultural backgrounds had similar high rates of anxiety post-MI: 46%, 35%, 43%, 52%, and 50% of patients in Australia, England, Japan, South Korea, and the US, respectively – a mean level of anxiety that was 77% higher than the normal mean level reported in a sample of healthy adults in each country. The authors concluded that patients suffering MI display a similar emotional response to this potentially life-threatening event, regardless of country of origin and culture. The association between MI and high anxiety held even after controlling for age, gender, marital status, education level, medical history, Killip classification on admission, the presence of comorbidities, use of therapies in the emergency department, and pain level – none of which interacted with country to affect anxiety. This finding is consistent with other research findings which indicate that "anticipation of physical danger" is a precursor to anxiety in both non-Western and Western cultures (87).

Data from the Moser and DeJong cross-cultural study was separately evaluated for gender differences in the presentation of anxiety across culture. Overall, women reported mean anxiety levels 25% higher than those reported by men – a pattern of higher anxiety in women that was seen in each country studied, which (according to the study authors) may account for poorer prognosis seen in women post-MI (88). Rates of anxiety in the general population are higher for women than for men, and women tend to suffer higher anxiety than men post-MI, a finding that is consistent across a variety of Western and Asian cultural groups (89).

There are several studies which find that anxiety predicts an increased risk of subsequent negative cardiac events for people who already have a diagnosis of CHD. A study by Frasure-Smith *et al*. of 220 AMI patients with a 1-year follow up found that patients with anxiety were 2.5 times more likely to suffer subsequent CHD events (i.e., reinfarction, unstable angina, CHD mortality) than patients with little or no anxiety (90). Moser *et al*. followed 86 AMI patients during their stay in the hospital for the incidence of recurrent ischemia, reinfarction, ventricular arrhythmias, and death and found that patients with high anxiety were 4.9 times more likely to suffer subsequent CHD events than patients with low anxiety (91). Denollet *et al*. followed 87 patients with a decreased ejection fraction after MI for 7.9 years and found that anxious patients were 3.9 times more likely than other patients to suffer subsequent MI, cardiac death, and unstable angina (92).

A study by Szekely *et al*. showed that preoperative anxiety was associated with greater morbidity and mortality following coronary artery bypass grafting and valve surgery, whereas preoperative depression was not (93).

In a different study by Moser and De Jong, 536 patients with AMI were followed after admission for in-hospital complications (reinfarction, ischemia, ventricular

tachycardia, ventricular fibrillation, or cardiac death) (94). This study found that patients with high anxiety had twice the occurrence of complications as patients with low anxiety, independent of age, diabetes, previous AMI, type of AMI, and Killip class. This study also found that the association between anxiety and CHD events was moderated by patients' "perceived control" over their own health. For patients with low perceived control, 20% experiencing low anxiety versus 80% experiencing high anxiety experienced complications. For patients with "high perceived control" there was no risk. In all these studies, anxiety was found to predict subsequent cardiac events independent of conventional risk factors and disease severity.

Up to 10% of patients suffer from post-traumatic stress disorder after MI, which interferes substantially with treatment compliance and leads to extremely poor outcomes (95).

Biological mechanisms fueling the adverse relationship between CVD and anxiety

The biophysical mechanisms whereby anxiety may contribute to the onset of CHD and negative CHD outcomes appear to be several and, as with depression, chiefly focus on the role of the SNS. Anxiety, both episodic and chronic, contributes to excessive activation of the SNS, and release of epinephrine, norepinephrine, and cortisol. Evidence suggests that both epinephrine and norepinephrine function as platelet agonists (96) and that epinephrine accelerates hemostasis and fibrinolysis (97). Patients with CHD and elevated anxiety or prolonged stress and a history of AMI have higher plasma norepinephrine levels (98). Similarly, patients undergoing cardiac catheterization manifest higher norepinephrine levels during mental stress testing (99). Patients with AMI and either ventricular dysrhythmias or sinus tachycardia have been found to have increased circulating catecholamine levels (100).

It has been found that patients with GAD have lower vagal tone than those with low levels of anxiety, which allows SNS activity to predominate (101,102). Research has also shown that anxiety can lead to increased blood cortisol levels that promote elevated resting blood pressure and heart rate (103).

Cardiovascular reactivity (CVR) is exaggerated in people with anxiety so that stressful stimuli can produce frequent, pronounced, and sustained changes in blood pressure, heart rate, stroke volume, and total peripheral resistance, which may then contribute to the etiology of heart disease and poor prognosis (104). Relatedly, in a study by Watkins *et al*. it was found that baroreflex control for AMI patients with high anxiety was about 20% lower than that for patients with lower anxiety (105). High anxiety is also associated with prolonged QTc intervals, and has been shown to increase risk for lethal cardiac dysrhythmias (106).

Even small, brief episodes of anxiety are hard on the heart and arteries. Mental stress ischemia (MSI) – the ability of low levels of anxiety or nervousness to provoke ischemia – is well documented. Mental stress increases heart rate and negatively affects the balance between myocardial oxygen supply and demand (107). For patients with atherosclerosis, a catecholamine surge caused by a stressful mental event can cause myocardial ischemia due to increased myocardial oxygen demand (108). Patients with CAD have exhibited larger increases in systemic vascular resistance during mental stress testing than during exercise (109[1]).

In a review article, Rozanski *et al*. compared mental stress-induced ischemia with exercise-induced ischemia, noting that both are associated with a sudden onset, smaller heart rate elevation, higher blood pressure, and lower double product (110,111). It appears that mental stress can induce ischemia at even lower levels of cardiac demand than exercise (112,113). Mental stress has been found to cause coronary artery occlusion (114) and AMI (115). Legault and colleagues reported that 49% of the patients they examined experienced stress-induced ischemia, patients with more severe coronary artery stenosis were the most likely to experience stress-induced ischemia, and stress-induced ischemia is often silent (116). Mental stress has also been shown to induce wall motion abnormalities and decreased LV ejection fraction in CAD patients (117). In addition, mental stress has been shown to cause coronary artery vasoconstriction in even normal coronary artery segments for people with and without CAD (118).

Stress-induced ischemic events may occur at relatively low heart rates, and as many as two-thirds of these events may go unnoticed by patients (119). While an array of negative emotions have been observed to trigger MSI, studies suggest that anger is the most potent trigger (120,121).

A study by Freeman *et al*. showed that patients who underwent coronary angiography experienced two time periods of stress: one highly stressful period while they awaited results of their procedure and a second less stressful period when they adjusted to their diagnosis and treatment plan. Patients experienced more episodes of silent ischemia during the first, more stressful period. Patients with higher levels of norepinephrine had more ischemic episodes, and their ischemic episodes lasted longer (122).

Patients with AMI who were exposed to mental stress testing experienced increased platelet aggregation, formed more circulating platelet aggregates, and developed higher plasma and serum thromboxane B2 levels than healthy controls (123). Patients with angina who underwent mental stress testing had higher rates of platelet activation than healthy controls (124). In a review article, von Kanel concluded that patients with atherosclerosis who experience anxiety and mental stress may tend toward hypercoagulation due to endothelial dysfunction and reduced fibrinolysis (125).

Mental Illness in Heart Transplant Patients – A Special Case

Several studies have examined the incidence rates for diagnosable depression and anxiety among patients waiting for heart transplant. Magni and Bogherini (126) found that 35% of patients waiting for heart transplant suffered from anxiety disorders and more than 20% suffered from marked depressive symptoms. Kuhn *et al.* (127) identified at least one psychiatric disorder in 63.8% of patients on the waiting list for transplant, Lang *et al*. in 48% of patients (128), and Trumper and Appleby in 39% (129). Major depressive episodes were the most frequent psychiatric disorder, followed by anxiety disorders. Similar high rates of postoperative depression and anxiety have been observed in the year following transplantation, with post-traumatic stress disorder being the primary diagnosis (130).

Subclinical Syndrome: Personality Type, Distress, and CVD

Substantial research has focused on the role that certain personality types have in the etiology and prognosis of CVD: specifically type A and type D personalities. These "personality types" by definition contain subclinical expressions of both depression and anxiety, referred to in the literature as *distress*.

Type A

Type A behavior pattern (TABP) or type A personality, first researched in the 1950s, is characterized by anger, hostility, impatience, a chronic sense of time urgency, excessive competitiveness, undue ambition, and social timidity. Type A personalities have been shown to have twice the risk for onset of CHD and higher rates of morbidity following diagnosis when compared to people of normal temperament and mood (131).

Type D

More recent research has focused on the type D personality, or "distressed personality." Type D personalities have a tendency toward negative affectivity (general, diffuse distress, and pervasive pessimism), a tendency to repress their feelings and ideas, and difficulty in social interactions. Type D people are often worried without specific reasons, often feel depressed and irritated, and rarely experience positive feelings. Their etiological risk for CHD is estimated to be twice as high as that for people with normal temperament and mood, and their relative risk of cardiac death following the onset of CHD almost three times higher (132).

An early study by Denollet and Brutsaert followed patients for a mean of 7.9 years after MI using the Millon Behavioural Health Inventory, with the purpose of investigating the association between type D personality and mortality after MI. The relative risk of cardiac death in patients with type D personality versus patients asymptomatic for depression and anxiety in this study was 4.3 (133).

Recent research into the "distressed personality" provides valuable insight into the remarkable clinical ramifications of subsyndromal mental distress. A recent meta-analysis of 9 prospective studies involving more than 6,000 patients concluded that, while many studies have confirmed the adverse relationship between clinical depression, anxiety, and CVD, the broader marker of "psychological distress" also predicts the development of CVD and also may account for part of the association of depression and anxiety with MI, poor cardiac prognosis, and autonomic cardiac dysregulation (134). In this meta-analysis type D personality was associated with a more than threefold increased risk of adverse events for patients with CAD. Studies involved in this analysis showed an odds ratio of ≥2.3 of adverse events for type D patients with heart failure (135), those receiving heart

transplant (136), and those with PAD (137).

Heart patients who suffer from subsyndromal mental distress are more prone to thrombogenesis, arrhythmogenesis, altered heart rate variability, increased platelet aggregation, increased myocardial oxygen demand, myocardial ischemia, impaired ventricular function, and cardiac dysrhythmias (138–140). MSI, covered previously in this article, is driven by fairly low levels of anxiety and nervousness typical for the general population, yet has disastrous consequences for the heart patient. Acute psychological insults, a single episode of rage for example, can stimulate SNS activity sufficiently to cause lethal ventricular dysrhythmias (141).

These research findings, taken collectively, indicate that subsyndromal mental distress poses a significant threat to heart health for the general population and is particularly toxic to patients who already have a diagnosis of CVD. Importantly, reducing patient distress has been shown to improve prognosis in patients with coronary heart disease (142).

Psychosocial Correlates of CVD, Stress, Depression, and Anxiety

The following psychosocial factors have been identified in the research literature as predictive for the etiology of CVD: depression, anxiety, stressful personality traits (i.e., type A and type D personalities), chronic stress, social isolation, and poverty (143–145). It is well-documented that the incidence of chronic stress, depression, and anxiety is higher among people of lower socioeconomic status (146).

Recognized psychosocial risk factors that contribute to higher morbidity and mortality rates in patients who already have a diagnosis of CVD include low socioeconomic status, social isolation, chronic family conflict, chronic job stress, acute stress, negative personality traits (i.e., hostility and anger, a tendency to repress emotions, type A and D personality), depression, anxiety, vital exhaustion, and negative behavior patterns like overeating, smoking, lack of exercise, and substance abuse (147).

Research shows that depression is a known cause or correlate of many of these established psychosocial and behavioral risk factors, namely less exercise, poor diet, obesity and smoking, especially in women (148), failure to use social support resources (149,150), and triple the risk of noncompliance with physician-ordered medical regimens (151). Anxiety, both clinical and subclinical, is also associated in the research literature with behaviors that are contraindicated for a healthy heart. Those with anxiety are more likely to eat an unhealthy diet, smoke, use drugs or alcohol or both, fail to adhere to physician instructions, experience sleep disturbance, and be physically inactive (152–154).

CVD Comorbidities: Hypertension, Metabolic Syndrome, and Diabetes

Chronic stress, depression, and anxiety, to varying degrees, are factors in the onset and severity of diagnoses that frequently co-occur with or presage CVD: hypertension, metabolic syndrome (MetS), and diabetes. There is some evidence that the presence of psychological comorbidities may promote progression of these disorders to CVD, though more research is needed in this area.

There is a substantial research base, nearly a century in the making, linking hypertension to negative affect, anxiety, depression, stress in general, and negative personality traits. Primary psychological factors linked to hypertension include generalized anxiety, depression, hopelessness, anger, suppressed hostility, defensiveness, lack of social support/social isolation, chronic stress, and type A behavior (155) with chronic negative emotions and chronic stress thought to be the most likely contributors. Research suggests that individuals who exhibit large increases in blood pressure during psychological stress when they are young are at risk for developing primary (essential) hypertension later in life (156). Independent studies also suggest that psychological stress is a strong determinant of behavioral risk factors that contribute to the onset of hypertension and its maintenance, to include smoking, obesity, poor diet, substance abuse, and physical inactivity (157–159).

Stress and depression are also proven correlates of diabetes. Stress-induced HPA hyperactivity increases inflammation and promotes hyperglycemia (160). Both chronic physical and emotional stress, especially chronically negative emotion, increase levels of cortisol and epinephrine, which can result in elevated blood glucose levels and greater insulin resistance. Acute stress of the sort experienced during hospital admission is well-known to produce hyperglycemia. Research suggests that patients 40 years of age and older who

experience hyperglycemia in response to acute stress are more likely to develop type 2 diabetes in subsequent years (161).

Depression and anxiety are fairly prevalent among people with diabetes. One well-controlled study of more than 600 diabetic patients participating in an urban outpatient diabetes education program found that 41.3% of participants had significant depressive symptoms and to be 41.3% and 49.2% had significant symptoms of anxiety (162). In a quantitative review of 20 studies conducted by Anderson *et al*. involving 2,858 patients with type 1 and type 2 diabetes, the point prevalence of major depression among diabetic patients was 26.1%, twice as high as among individuals without diabetes (163). Depressed diabetic patients have been shown to have higher ambulatory care use, fill more prescriptions, and utilize up to 4.5 times as many financial resources for their treatment than nondepressed diabetic patients (164). Egede *et al*. studied 10,025 men and women over 8 years and found that comorbid diabetes and depression are associated with significantly increased all-cause death compared to all-cause death from either alone (165). Clouse *et al*. in studying diabetic women found that major depression was an independent risk factor accelerating the development of CHD (166).

Depression and distress are associated with MetS in the research literature, though more research needs to be done on this association. The Third National Health and Nutrition Examination Survey in the US – a large-scale longitudinal study involving 3,186 men and 3,003 women aged 17–39 who were free of CHD and diabetes at the start of the study – found that women with a history of a major depressive episode were twice as likely to develop MetS compared with those having no history of depression (167). This relationship remained after controlling for age, race, education, smoking, physical inactivity, carbohydrate consumption, and alcohol use. In this survey, men with a history of depression were not significantly more likely to develop MetS.

A study by Skilton *et al*. that followed 1,598 men and women at risk of CVD for associations among MetS, anxiety, and depression found that the number of components of the MetS increased with increasing levels of depression but not anxiety, an association that was independent of age, smoking, body mass index, socioeconomic factors, and lifestyle (168). In a small but well-controlled study by Heiskanen *et al*., 121 depressive outpatients were followed for a period of 6 years for severity of depressive symptoms, general psychopathology, and development of MetS. At 6-year follow up the prevalence of MetS in the study group was 36%. MetS was associated with a current diagnosis of major depression and overeating, but not with age or sex (169).

Vitaliano *et al*. found that older men followed a psychophysiological pathway from chronic stress to distress to the metabolic syndrome to CHD (170). Older women showed the same pattern but less severe, and older women using hormone replacement therapy (HRT) did not show this pathway. Vaccarino *et al*. found that both depression and metabolic syndrome were significant predictors of CVD and that metabolic syndrome explains only a small portion of the association between depression and CVD (171).

In another study by Skilton *et al*., 1,598 subjects at risk of CVD were assessed for metabolic syndrome, depression, and anxiety to investigate whether metabolic syndrome is associated with anxiety or depression, whether these relationships vary by gender, and whether they are independent of age, obesity, smoking status, socioeconomic factors, and lifestyle (172). This study concluded that metabolic syndrome is associated with depression and depressive symptoms, but not statistically significantly associated with anxiety, irrespective of gender, and obesity in subjects at risk for CVD.

The Continuum: Stress, Distress, and Clinical Depression and Anxiety

Chronic stress is now believed to be the leading cause of depression (173) and acute stress, especially if it is encountered in childhood, the most significant factor in the development of anxiety disorders and depressive disorders later in life (174). Individual susceptibility to this continuum is mediated by specific biomarkers and genetic characteristics, by the individual's ability to engage in healthy coping strategies (i.e., regular exercise), their reliance on social support systems and their access to effective treatment. There are different types of anxiety and depression and these disorders can be caused by factors other than stress (i.e., neuroendocrine pathology, traumatic brain injury, stroke, congenital factors), but up to 85% of all cases of clinical depression and anxiety are now thought to result from stress (acute and chronic), biological vulnerability to its onslaught,

coping skills applied along the continuum, access to social support, and the availability of effective clinical care.

Science long ago proved that stress is actually necessary and helpful to our evolution as a species. Without it we would not develop the skill and resilience we need to thrive. However, it is important to draw a clinical distinction between ordinary stress, known as *eustress* in the scientific literature, and *distress*. With eustress a person feels challenged, agitated, or fearful, the HPA axis triggers SNS activity but the biological stress response is short in duration and it resolves quickly after the stressor is passed and/or appropriate coping skills are applied. By contrast, distress is a harmful, intense emotional and biological stress reaction that does not resolve without significant intervention and persists even in the absence of current stressors. Chronic stress and acute stress induce the neurobiologic changes that lead to distress, depression, and anxiety.

Exposure to adversity has long been associated with the risk of psychiatric disorders. Recent research in humans shows that cumulative exposure to adverse life events is associated with smaller gray matter volume in key prefrontal and limbic regions of the brain involved in stress, emotion and reward regulation, and impulse control (175). Acute stress encountered early in life (i.e., psychological or physical abuse, death of a parent) has been shown to result in increased and long-lived hyperactivity of corticotropin-releasing factor systems that promote increased reactivity to stress across the lifespan (176). This phenomenon is well-known in the disciplines of clinical psychology, neuropsychology, and psychiatry and substantial current research is focused on strategies to prevent or reverse the detrimental effect of early life stress on the CNS.

Equally well-researched are the serious neuropsychiatric and health consequences of repeated exposure to acute stress. For example, there is a large body of research evidence linking combat stress with persistent HPA hyperactivity, reductions in functional connectivity between the midbrain and prefrontal cortex, and significant impairment to memory and cognition, all of which are markers for post-traumatic stress disorder (177), which is very highly correlated with the etiology of CHD and high rates of CHD-related morbidity and mortality (178).

Chronic psychosocial stress is a known factor in the etiology and course of CVD but is often dismissed in clinical settings. In the INTERHEART case-control substudy of MI in 52 countries, psychosocial stress was reported to account for approximately 30% of the risk of MI (179). In one very large scale epidemiological study, Kershaw *et al*. analyzed data for 82,000 women from the Women's Health Initiative Observational Study to estimate associations between stressful life events (SLE) and social strain with CHD and stroke. The study authors found that higher SLE and higher social strain were associated with a higher incidence of CVD and hemorrhagic stroke, independent of sociodemographic factors and depressive symptoms (180).

Chronic stress has been shown to sustain HPA hyperactivity even in the absence of current stressors, increase production of corticoids, cause neuronal death, reduce hippocampal size and density, alter feedback pathways in the brain, lower levels of serotonin, and reduce levels of brain-derived neurotropic factor (181–183). A recent review of the research in this area by N. Rohleder concluded that repeated psychosocial stress causes and sustains low-grade systemic inflammation, which plays a key role in the pathophysiology of CVD, and further, that lower subjective social status and perceived limits surrounding pursuit of purpose in life are associated with increased inflammatory responses to repeated stress exposure (184).

A longitudinal study by Johansson *et al*. followed a cohort of 1,462 women aged 38–60 years for more than 30 years to assess the effects of mid-life psychosocial distress on late-life health. Study participants were regularly interviewed for stress symptomology and received CT examinations in 1968, 1974, 1980, 1992, and 2000. This study found that women who reported frequent or constant distress at one or more examinations in 1968, 1974, or 1980 developed moderate-to-severe white matter lesions and moderate-to-severe temporal lobe atrophy by 2000 (185).

More than a dozen potential biomarkers that interact with stress to promote the etiology of clinical depression and anxiety have been identified, including monoamine regulators, proinflammatory cytokines, and other inflammatory mediators, mediators of glutaminergic activity, and GABAergic activity, as well as regulators of neurogenesis (186). In one very recent study by

Owens *et al*., 1,858 teenagers were followed over 3 years for the symptoms of depression. This study found that teenage boys who had some depressive symptoms at the start of the study, together with high levels of circulating morning cortisol (as measured in their saliva) were 14 times more likely to develop major depression within the following 3 years than boys without any signs of depression and low levels of cortisol, and 2–4 times more likely to develop clinical depression than boys with *either* depressive symptoms *or* high levels of morning cortisol. Girls with some depressive symptoms and high levels of cortisol were 4 times more likely to develop major depression within 3 years than same-age girls who had no symptomology and low cortisol levels at the start of the study (187).

Guintivano *et al*. recently identified an epigenetic and genetic biomarker for suicidal tendencies (a frequent symptom of severe depression) – a mutation in the *SKA2* gene. In this study, researchers found the *SKA2* mutation was associated with higher levels of cortisol and glucocorticoids and significantly interacted with chronic stress and anxiety to explain about 80% of suicidal behavior and progression from suicidal ideation to suicide attempt (188).

As previously described, *distress* is a known cause of cardiovascular pathology. One model of the relationship between mental status and heart disease etiology suggests that subsyndromal psychological factors previously considered benign – that is, anger, hopelessness, low self-esteem, chronic worry – are sufficient to trigger production of catecholamines, sustain HPA hyperactivity, increase heart rate and blood pressure, decrease plasma volume, constrict coronary arteries, and increase cardiac demand, platelet activity, coagulation, and inflammation (189).

Table 1 provides list of the most common symptoms of stress and Table 2 the list of clinical criteria for depression and anxiety. On observation, the symptoms for depression and anxiety are nearly identical to the symptoms of stress. The difference between

Table 1. Signs and symptoms of Stress

Psychological Symptoms	Physical Symptoms	Behavioral Symptoms
Poor memory/forgetfulness	Dry mouth	Under- or overeating
Inability to concentrate	Enlarged pupils	Isolating yourself from others
Confusion	Sweating or blushing	Angry or irrational outbursts
Excessive worry	Motor agitation or restlessness	Crying, or feeling like you want to cry
Irritability	Inability to relax	Procrastinating
Impatience	Jaw clenching	Neglecting your responsibilities
Anger	Frequent headaches, backaches, neck aches	Conflict in relationships
Poor judgment	or body aches	Relying on alcohol, drugs or tobacco
Seeing only the negative	Diarrhea, constipation, heartburn or stomachache	Nervous habits (nail biting, fidgeting, pacing)
Racing thoughts	Nausea	Uncharacteristically poor performance
Negative, ruminative thinking	Sleeplessness	Excessive overwork
Moodiness	Heart palpitations	Mumbled speech
Feeling overwhelmed	Rapid heartbeat	Excessive impulse buying
Feeling lonely and isolated	Chest pain	Lying to cover-up poor performance
Sadness	High blood pressure	
Feeling insecure or fearful	Dizziness/lightheadedness	
Anxiety (see Table 2)	Loss of sex drive	
Depression (see Table 2)	Frequent colds and flu	
	Sleeping way too much or way too little	

stress symptomology and the clinical criteria for a psychiatric diagnosis lies primarily in symptom volume and chronicity. At least five of the symptoms on the Table 2 checklists must be present nearly every day, most of the time, in order to make a diagnosis of clinical depression or anxiety. Patients who meet these criteria are then assessed for symptom severity to determine whether their clinical presentation is mild, moderate, or severe.

People who have four or fewer symptoms from the checklists in Table 2 are considered subsyndromal, regardless of symptom severity. Subsyndromal depression and anxiety is very frequently seen in patients with heart disease and, as previously cited, these *distressed* patients are more than twice as likely to develop CVD and up to three times more likely to have a poorer prognosis than patients with normal mood (190).

Table 2. Anxiety and Depression – distress in the extreme

Anxiety	Depression
Five or more of these symptoms that persist for at least 2 weeks:	Five or more of these symptoms that persist for at least 2 weeks:
■ Excessive, ongoing worry	■ Feelings of worthlessness
■ Restlessness or motor agitation	■ Sadness all day, nearly every day
■ Exaggerated view of problems	■ Loss of interest in favorite activities
■ Irritability	■ Loss of interest in sex
■ Anger	■ Excessive feelings of guilt
■ Muscle tension	■ Difficulty focusing or concentrating
■ Headache, backache or neck ache	■ Feelings of restlessness
■ Sweating	■ Thoughts of death or suicide
■ Difficulty focusing or concentrating	■ Trouble making decisions
■ Nausea or heartburn	■ Fatigue or lack of energy
■ Sleep disturbance	■ Sleeping too much or too little
■ Bouts of tiredness	■ Unintentional change in weight
■ Frequent urination	■ Bodily pain, usually muscular
■ Trembling	■ Psychomotor agitation
■ Being easily startled	

Source: The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (191).

Anxiety and depression have symptoms in common but overall their symptoms exhibit distinct central tendencies: anxiety is usually accompanied by excessive, exaggerated worry about everyday events and hyperactivity, while depression tends to be dominated by feelings of sadness, guilt, lack of self-worth, in-activity, and withdrawal.

Research evidence suggests genetic and neurobiologic similarities between depressive and anxiety disorders, many of which have been reviewed in this article. It is quite common for patients with clinical depression to have symptoms from the anxiety checklist and vice versa. Approximately 85% of patients with depression also have significant symptoms of anxiety, an association that holds true for men in the particular, and significant depressive symptoms occur in up to 90% of patients with anxiety disorders (192,193). Although depression and anxiety symptoms co-occur with great frequency and they share a substantial component of general affective distress, they can be differentiated based on factors specific to each syndrome (194).

It should be noted that a substantial number of patients satisfy full diagnostic criteria for *both* depression and anxiety, evidencing true comorbidity. The most frequent comorbid psychiatric diagnosis in the US is MDD and GAD. Based on analysis of two massive data sets – the National Comorbidity Survey and the Midlife Development in the United States Survey – comorbidity of this type occurs in more than 58% of individuals with either diagnosis (195). By and large these patients have

a more protracted course of illness and respond less well to therapy (196).

Frasure-Smith and Lesperance assessed the prognostic importance of MDD and GAD together with self-reports of anxiety and depression and their co-occurrence during 2-year follow up of 804 men and women with stable CAD, measuring incidence of major adverse cardiac events or MACEs (cardiac death, MI, cardiac arrest, or nonelective revascularization) in the 2 years following baseline (197). They found that anxiety and depression both predict greater MACE risk in patients with stable CAD. By contrast, Strik *et al*. examined male-only patients with established CHD and followed them for 3.4 years to examine the relative impact of symptoms of depression versus anxiety on prognosis. This study found that anxiety symptoms were the strongest predictor of future negative cardiac events, rehospitalization, and increased healthcare consumption for men (198).

A very recent study of 556 outpatients with HF by Dekker *et al*. found that one-third of all patients had both depressive and anxiety symptoms, and that patients with higher levels of depressive symptoms also experienced a higher level of anxiety symptoms. This study found that younger age at onset of HF and depressive symptoms were independent predictors of anxiety (199).

An Epidemic of Stress, Depression, and Anxiety

It is remarkable that depression, in and of itself without any specific comorbidity, is associated with a decrement in health status almost as bad as the decrement associated with congestive heart failure after each group is adjusted for the presence of comorbidities (200). Physical function and general health are also lower for depressed patients compared to patients with other chronic diseases such as diabetes and CAD. The excessive morbidity associated with depression is well-documented in the scientific literature, but its implications have been largely ignored by mainstream medicine until recently, owing to unprecedented increase in rates of depression, anxiety, and distress worldwide. The World Health Organization (WHO) estimates that, owing to the rise of chronic stress globally, depression has become a pandemic. By 2030 it is expected to be the number one leading cause of disease burden worldwide, eclipsing even heart disease (201).

Mental problems are grossly under-reported owing to the stigma associated with mental illness, and this is especially true for India, whose honorable, dutiful, intelligent populace tends to view mental instability as a personal failure. Unfortunately, high rates of chronic and acute stress, a cultural disdain for seeking help with mental problems, and a lack of early intervention and treatment alternatives have combined to fuel an epidemic of depression and anxiety in India. According to a substudy of the WHO World Mental Health Survey Initiative in 2011, India's lifetime prevalence rate for major depressive episodes is 35.9% – the highest in the world, more than three times as high as the 11.1% average for other developing countries and more than twice as high as the lifetime prevalence rate for depressive episodes in the US (202). In this study, the incidence of depressive episodes was higher for women than for men by a ratio of 2:1, which also holds true in the US (203). Doctors from The National Institute of Mental Health and Neurosciences and leading psychiatrists in private practice report that the incidence of depression is rising precipitously, especially in urban areas, where the current point prevalence of depression among Indians is estimated to be 10% (204).

Suicide rates – a key indicator of the prevalence of major depression – are increasing among India's youth and young adults, consistent with the pattern for developed nations. According to the National Crime Records Bureau of the Indian Ministry of Home Affairs, 135,445 people committed suicide in India in 2013 and of these, 68% were between the age of 15 and 29 (205). Suicide is the third leading cause of death among teenagers worldwide, following accidents and AIDS.

While there are no reliable nationwide data on rates of anxiety in India, limited data from the WHO place the current point-prevalence rate of GAD at 8.5% (206). Senior fellows at the National Institute of Mental Health and Neurosciences estimate the point prevalence for anxiety disorders to be 20–25%, or one out of every four or five Indians (207).

The escalating incidence of mental illness in India is a function of several economic and cultural factors. Chief among these is the rise of chronic stress. India is now considered to be the stress capital of the world, eclipsing even Japan and the US for this dubious honor. In pursuit of superpower status and lifestyle, a majority of Indian companies and employees are making unhealthy tradeoffs. The Indian Council for Research

on International Economic Relations reports that India's rapid expansion has boosted corporate profits and employee incomes but caused a surge in work-related stress and lifestyle diseases, and that most Indian companies are doing nothing to tackle the problem (208). The recent economic downturn caused a spike in employee stress due to fear of job loss and "lack of perceived control" – key factors in perception that are a principle trigger for chronic SNS activation.

The Regus Work-life Balance Index for 2013, which surveyed more than 26,000 professionals in more than 90 countries, ranked India second-worst in the world (second only to Mexico) for poor work–life balance, high rates of work-related stress, and frequency of stress-related illness (209). In this survey, respondents labeled work problems, personal finances, commuting to work, and instability in the world economy as the chief reasons for their increasing stress.

The picture for India's women is more complicated. Research shows that psychosocial risk factors for mental illness that disproportionately affect women include gender-based violence, socioeconomic disadvantage, low income and income inequality, low or subordinate social status and rank, and responsibility for the care of others (210). India's women are disproportionately affected by all these risk factors, and this is clearly reflected in their stress levels: according to Nielsen's "Women of Tomorrow" survey conducted in 2011, 87% of India's women are severely stressed, the highest of any nation (211). In this survey, working women of India reported that their stress is chiefly due to two factors: (i) they are allowed autonomy and decision-making power in the workplace, but are still expected to be subservient to their husbands/men in all other aspects of life, and (ii) relative to their husbands, they shoulder almost all the responsibility for maintaining their households and raising children, even though they work full time.

Increasing rates of chronic stress, distress, depression, and anxiety in India should be of great concern from both the clinical and public health perspectives.

Effective Intervention

Depression, anxiety, and distress in the cardiac patient can be treated effectively, even cured, resulting in vastly improved cardiovascular health and reduced risk of future adverse cardiac events and lower utilization of costly health and allied health services (212). The science base regarding effective treatment for this population is rich and getting richer every day, demonstrating that the gold standard of care for this population is *integrative medicine*: the combination of allopathic care and mind-body medicine.

Mind-body medicine – use of the mind to heal the body and vice versa – is a well-established medical discipline in the US and Europe. Mind-body medicine is a multidisciplinary approach that involves medication, psychotherapy, clinical hypnosis, psychosocial support (usually in groups), proven stress reduction techniques like meditation and yoga, regular aerobic exercise, and a heart-healthy diet combined with targeted nutrition for the heart (i.e., nutraceuticals like C0Q10). Mind-body medicine combines clinical therapies and healthy lifestyle elements to reverse the genetic, biophysical, and mental determinants of illness, foster superior mental and physical health, and create resilience to stress and stress-induced illnesses.

Institutions that specialize in integrative medicine, like The Benson-Henry Institute of Mind-Body Medicine at Massachusetts General Hospital (the number one-ranked hospital in the US) have established the remarkable effectiveness of mind-body medicine in the treatment and prevention of heart disease and other stress-related illnesses. Dr. Herb Benson, founder of the Benson-Henry Institute and considered to be the father of mind-body medicine in the US, is a cardiologist who pioneered meditation research for its healthful effects on the cardiovascular system in the 1970s (213,214).

It won't be lost on the reader that the basic tenets of mind-body medicine are analogous to those of the yogic lifestyle, which is highly effective in the prevention and treatment of heart disease, chronic stress, and stress-related illnesses. Manchanda *et al*. found that a yoga protocol which included health-rejuvenating exercises, breathing exercises, yoga postures, and meditation, when added to basic healthy lifestyle elements of a vegetarian diet and regular exercise, reverses early atherosclerosis in metabolic syndrome. In addition, the yoga group showed greater reduction in BMI, waist circumference, LDL-C, and systolic blood pressure (215). Gupta *et al*. studied the effect of a similar multidimensional intervention, the Happy Lifestyle (HLS) program, on regression of coronary atherosclerosis and reduction in cardiac events in an open trial involving 123 angiographically documented moderate to severe CAD patients. HLS

included a low-fat, high-fiber vegetarian diet, moderate aerobic exercise, and stress management through Rajyoga meditation. At 2-year follow up, subjects with the most adherence to the HLS program had experienced slightly more than 18% ± 12 absolute percentage points diameter stenosis regression and substantial reduction in cardiac events compared to subjects with the least adherence to the study protocol. Study authors concluded that more than 50% adherence to the HLS protocol was essential to achieve a significant change (216).

Relatedly, Dr. Jon Kabat-Zinn in the US developed the MBSR, a mindfulness-based stress reduction program involving mild forms of Hatha Yoga in combination with meditation, exercise, and a healthy diet, which demonstrated statistically significant levels of stress-reduction, positive changes in brain activity, improved emotional processing, better immune functioning, better circulation, and other symptom reduction in people who suffer from heart disease and breast cancer (217,218). Over 200 medical centers and clinics in the US and Europe now use MBSR Dr. Kabat-Zinn's approach for their patients who suffer from stress-related illnesses.

In recognition of a growing body of research evidence demonstrating the effect of the mind on bodily health, the field of clinical psychology developed a specialty called *Health Psychology,* and in 1977 *health psychology* became a division of the American Psychological Association. The last two decades have seen the emergence of subspecialties like cardiac psychology and oncological psychology (referred to in Europe as "psychocardiology" and "psycho-oncology"). It appears that health psychology's association with each major disease is characterized by unique and specific theoretical and methodological characteristics, and there is debate in the field of medicine as to whether these subspecialties should be considered part of clinical psychology or as new, autonomous medical disciplines (219).

CVD is a multifactor problem that requires a multifactor solution, and the same is true for depression, anxiety, and subsyndrome distress. In cardiac psychology, the right treatment approach is based on a differential diagnosis of patient need across several domains: symptomatology, physical functionality, psychological status, psychosocial history, cardio history, cardio disease perception and processing, financial and other resources, coping skills, self-efficacy, family and social support, motivation toward recovery, attitudes toward adherence to physician-recommended therapies and procedures, and expectations (220).

Assessment

Cardiologists and other medical specialties, as well as doctors who work in primary care settings, are generally not eager to function in the role of a mental health professional, nor do they have the time and resources. To answer this challenge, a great deal of research has been devoted to depression and anxiety screening instruments that are valid, specific, and *brief*.

In 2008 The American Heart Association published physician guidelines for the diagnosis and treatment of depression in heart patients (221). It suggested the use of the two-question Patient Health Questionnaire, or PHQ-2 for use in busy primary and specialty healthcare settings. The PHQ-2 is self-administered by the patient and can be scored by a nurse or admitting staff member. It reads "Over the past 2 weeks, how often have you been bothered by either of the following problems?

- Little interest or pleasure in doing things.
- Feeling down, depressed, or hopeless."

The patient rates their response to each question using a simple 4-point scale:

Not at all (score 0), Several days (score 1), More than half the days (score 2), Nearly every day (score 3). The total PHQ-2 score can range from 0 to 6. A score of 3 or more has been shown to have a sensitivity of 83% and a specificity of 92% for major depression (222)[2; 3 is considered the optimal cut-point for further screening and a score of 0 virtually excludes depression.

AHA guidelines recommend that patients who score 3 or more on the PHQ-2 be screened with the PHQ-9, a 9-question screener which has been validated in more than 6,000 patients (223). Despite its brevity, the PHQ-9 provides the sensitivity and specificity needed for assigning a provisional diagnosis of depression. It also provides a severity measure for treatment planning purposes, serves as a diagnostic instrument for the depression criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (the DSM IV), and it has been proven accurate for patients with CAD (224,225). Like the PHQ-2, it is self-administered by the patient and can be scored in moments by a nurse or staffer.

Given the popularity of the two-stage PHQ series for assessing and monitoring depression, similar 2- and 7-step anxiety screeners were developed by Spitzer *et al*. and subsequently validated in 2,740 primary care patients (226). This series is called the GAD-2 and GAD-7, respectively, with GAD meaning generalized anxiety disorder . Like the PHQ series, the GAD screeners are patient self-administered and can be scored by a nurse or staffer in moments. The GAD-2 asks: "Over the past 2 weeks, how often have you been bothered by the following problems:

- Feeling nervous, anxious or on edge
- Being unable to stop or control worrying"

The patient responds using the same 4-point scale used in the PHQ: Not at all (score 0), Several days (score 1), More than half the days (score 2), Nearly every day (score 3). The total possible score on the GAD-2 is 0 to 6. A score of 3 or higher warrants assessment with the GAD-7, which provides severity measures across all 7 diagnostic criteria for anxiety in the DSM IV. The GAD-7 has a total possible score ranging from 0 to 21. Scores of 5, 10, and 15 represent cut-points for mild, moderate, and severe anxiety respectively. When screening for anxiety disorders, the recommended cut-point for further evaluation is a score of 10 or greater, which has a sensitivity of 89% and specificity of 82% for GAD. Although originally developed to diagnose GAD, the GAD-7 is also proven to have good sensitivity and specificity as a screener for panic, social anxiety, and post-traumatic stress disorder (227).

A recent trend in cardiology practice in the US is to combine elements from the PHQ and GAD screeners into a single short-form "patient coping" survey (228). More research is needed to refine these instruments. In the meantime, the PHQ and GAD screeners yield valid results and can be administered with little or no staff time and resources. Both series are in the public domain and easily accessible via the web at no cost.

The underdiagnosis of depression in cardiac care is highly significant, greater even than in primary care settings, where doctors fail to diagnose depression more than half the time. Kop and Ader list the top reasons why this may be true: underestimation of depression's effects on adverse cardiovascular outcomes, the atypical nature of depression in cardiac patients, belief that depressed mood is "normal" given the patient's medical condition, time constraints for appropriate assessment, avoidance of social stigma associated with depression, and unawareness of treatment options (229).

Studies have shown that the symptomology of depression in cardiac patients often differs from that observed in general psychiatric patients. Complaints of tiredness or lack of energy are more frequent for people who suffer from heart disease and depression, whereas melancholy or depressed mood states are more common for psychiatric patients in general (230–232). Estimates of the point prevalence of vital exhaustion in patients with CAD range from 20% to 45% (233). Vital exhaustion in cardiac patients is very similar to the exhaustion observed in patients with "vegetative depression" – a severe form of depression – which may also account for the underdiagnosis of depression among cardiac patients.

For all these reasons, a valid, objective screening procedure is a must in the cardiac setting. There is some debate regarding "when" to screen heart patients for depression and anxiety. Many doctors are reticent to screen for mental disorders if they have no reliable resources for patient referral and treatment for these problems. Recent research has provided clarity on this dilemma, however, and the evolving consensus among medical professionals is to screen patients as early as possible, regardless of whether mental health treatment options are available.

To assess the benefits of screening, Smolderen *et al*. conducted a prospective study of 4,062 AMI patients from 24 US hospitals. All patients completed the PHQ-9 during their index AMI admission. Depressed patients were then randomly assigned to one of two conditions: unrecognized versus recognized. Depression was "recognized" by the hospital treating team if it was documented in the patient's chart (a depression diagnosis, discharge antidepressants prescribed, and/or referrals for counseling). Follow-up interview data on patient use of antidepressants and counseling were collected at 1 and 6 months but otherwise the cardiac care team was uninvolved in mental health service delivery or case coordination. At 1 year after discharge mortality was compared between "recognized" versus "unrecognized" depressed patients and nondepressed patients. Results were that AMI patients with "recognized" depression had survival rates similar to those of nondepressed patients (6.1% and 6.7%, respectively) compared to a

10.8% mortality rate for patients who were depressed but whose depression was unrecognized. Patients whose depression was "recognized" received more depression treatment on their own post-discharge than "unrecognized" depressed patients (70% vs. 24%, respectively) (234).

In the majority of cardiology practices in the US, a cardiac patient with positive screening results for depression, anxiety, or distress is referred for evaluation to a mental health professional who is qualified in the diagnosis and treatment of these disorders. That professional then makes a specific diagnosis and provides relevant treatment. He or she is also responsible for coordinating patient care with the cardiology practice. The AHA recommends, based on research evidence, that patients with heart disease who are being treated for depression (and anxiety) should undergo careful monitoring for adherence to their medical treatment regimen, and for the efficacy and safety of drug therapy for their medical and mental health conditions (235).

Treatment Modalities

Ideally, treatment of depression and anxiety in cardiac patients should be based on a differential diagnosis of patient need within the larger framework of mind-body medicine, using a multifactor approach, and treatment should be formulated using evidence-based modalities. The modalities which have been demonstrated effective for this population are pharmacotherapy, psychotherapy, clinical hypnosis, meditation, exercise and somatic relaxation techniques, support groups, cardiac rehabilitation, and case management. These modalities are reviewed briefly here.

Pharmacotherapy

Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Serotonin Antagonist and Reuptake Inhibitors (SARIs), and benzodiazepines are considered the prescriptive choice for people with depression and anxiety in the general population. Of these, safety for heart patients has been examined in clinical trials for fluoxetine and sertraline (236–238), citalopram (239)[^{2}, and mirtazapine (240). The strongest evidence of safety is for SSRIs, sertraline in particular (241).

In the majority of cardiac settings, treatment for depression and anxiety is still mostly limited to the dispensing of SSRI medications, despite their limitations and recent challenges to their efficacy. SSRIs have long been under scrutiny for efficacy and reliability. SSRIs work on average less than 50% of the time and when they do work, efficacy can range from almost no effect to the remarkable, showing tremendous variance among individuals, hospitals, and clinics. As early as 1964 Greenblatt *et al*. showed that, among two institutions, one had a 31% success rate using SSRIs while another had a 67% success rate using the same medications and clinical criteria (242). Recently, a major meta-analysis by the American Medical Association demonstrated that SSRIs do not work any better than placebo (243). Interestingly, with increasing marketing investment by pharmaceutical companies, the SSRI placebo effect in the US more than doubled from 1980 to 2005 (244). Relatedly, it appears that a stronger doctor–patient relationship will produce greater benefit in patients taking SSRIs (245,246). However, it remains that SSRI effects are nothing more than placebo.

Original SSRI research was based on the theory that the brains of depressed people, due to congenital or other factors, are low in serotonin, but science was never able to measure this to prove that it is true (247). Recent research, reviewed in prior sections of this article, shows that serotonin depletion is but one of multiple neurobiologic effects of chronic distress, depression, and anxiety. An SSRI, while a helpful adjunct to the treatment of depression, major depression especially, does not target the most frequent underlying cause of depression: mental distress and stress-related neuroendocrine pathology. For all these reasons, the standard of practice for major depression requires both psychotherapy and anti-depressive medication to be administered.

There is some evidence that SSRIs may improve depressive symptoms and reduce the frequency of reinfarction and death due to MI for extremely depressed patients with CAD, but they do not render these benefits with consistency. The Enhancing Recovery in Coronary Heart Disease Patients Randomized Trial (ENRICHD) evaluated 2,481 individuals within 28 days of MI with a mean follow up of 29 months. Patients with depression were randomized into a protocol that included low-intensity cognitive behavioral therapy (CBT) (6 individual and group sessions over 11 weeks). Patients who showed less than a 50% reduction in Beck Depression Inventory scores after 5 weeks of CBT were referred to a psychiatrist for pharmacotherapy, usually

sertraline. This study found no statistically meaningful reduction in late mortality (death ≥ 6 months following MI) for the study population overall (248)[2; however, a subpopulation of patients with severe depression who showed great benefit from the intervention in terms of reduced depressive symptoms showed a statistically significant 43% reduction in frequency of reinfarction and/or death due to CHD during follow up.

The Sertraline Antidepressant Heart Attack Trial (SADHART) claimed that sertraline (Zoloft) was safe to use for heart patients, based on no statistically significant differences in cardiac function at the end of a 24-week follow up for patients who had been hospitalized after MI or unstable angina. Depressed patients who received sertraline experienced fewer severe adverse cardiovascular events (another MI, stroke, or death) during follow up than depressed patients in the control group. However, based on small sample size (369 patients) and short duration of follow up, it is not possible to generalize these findings (249). Indeed, subsequent analysis of data from SADHART showed that treatment with sertraline compared with placebo did not support improved cardiovascular status among patients with depression at statistically significant levels (250).

In the Canadian Cardiac Randomized Evaluation of Antidepressant and Pychotherapy Efficacy (CREATE), 284 patients with chronic CHD and MDD (a score of 20 or more on the 24-item HAM-D) were randomly assigned half to the SSRI citalopram, and half to placebo. Citalopram showed antidepressant efficacy (reduction of depressive symptoms) in some patients and no evidence of harm, but also failed to show any statistically significant improvements in cardiovascular health for study participants (251).

Apart from questions regarding efficacy and reliability, SSRIs have mild cardiotoxic effects, to include increased heart rate and reduced heart rate variability (252) and they alter the activities of cytochrome P450 (CYP) liver enzymes involved in the metabolism of drugs frequently prescribed for heart patients, including but not limited to β-blockers, warfarin, type1 antiarrhythmics, and calcium antagonists (253). Following AMI especially, patients taking anticoagulant therapy and SSRIs run a higher risk of bleeding (254). Heart patients who take these medications must therefore be closely monitored.

Most of the studies on medication therapies for heart patients have focused on safety, not efficacy. Based on research evidence, tricyclic antidepressants (TCAs) are specifically contraindicated for heart patients because they can produce quinidine-like cardiotoxic effects that include QTc prolongation, conduction delay, block of the A-V conjunction and bundle branches, bradycardia, tachycardia, atrial or ventricular arrhythmia, cardiac arrest, ST-T abnormalities, MI, and exacerbation of heart failure (255,256).

SARIs and benzodiazepines – medications that are a prescriptive choice for anxiety disorders and depressive disorders with coexisting anxiety in the general population – have not been fully evaluated for safety in heart patients. Cardiac arrhythmias and QT prolongation have been reported with SARI use and they are specifically contraindicated for patients during the initial recovery phase following MI (257). Although benzodiazepines have long been prescribed for short-term use by the post-MI patient to reduce anxiety, there are no controlled trials documenting the benefits of this protocol (258) and recent research suggests that sustained use of benzodiazepines may contribute to heart failure and cardiac death (259).

Psychotherapy

In the hands of a properly trained doctoral-level clinician, psychotherapy can reverse the neurobiologic and psychological consequences of chronic stress, depression and anxiety, is preferred over medication therapy by many patients, and can be combined with medication to increase medication efficacy in patients with more severe psychiatric diagnoses (260).

Along with medication therapy, CBT was used in ENRICHD (261), IPT was used in CREATE (262), and problem-solving therapy in the Coronary Psychosocial Evaluation Studies (COPES) (263,264). In all these trials, patients suffering from CHD and psychological disorders experienced treatment efficacy (remission of psychological symptoms) but little statistically meaningful reduction in coronary morbidity and mortality. However, in trials like these where drug efficacy and safety are foremost in research design and analysis, psychotherapy is provided at very low levels of intensity, and it is considered a "drug trial confounder," along with patient education and supportive care (i.e., frequent visits and telephone follow up by a caseworker who is monitoring for psychiatric symptoms), so it is

impossible to examine the efficacy of psychotherapy as a stand-alone therapy in these types of studies (265).

To look at psychotherapy's effectiveness in heart patients we turn to two major meta-analyses of psychosocial intervention for depressed patients with CHD by Dusseldorp *et al*. (266) and Linden *et al.* (267), which showed a reduction in all-cause mortality and cardiac morbidity for depressed and anxious patients who received intervention. The Recurrent Coronary Prevention Project, in which 1,013 MI patients with depressive symptoms were randomly assigned to receive psychotherapy and social support, showed a reduction in depressive symptoms and a 44% reduction in cardiac death and nonfatal MI for the treatment group (268). These findings are startling given the low frequency and intensity of psychosocial intervention typically employed in randomized trials.

Psychotherapy works well to improve the health and longevity of cardiac patients, but the resources (human and financial) needed to provide it at sufficient levels of intensity are typically only available for the upper classes. Indeed, the chief reason there is little research basis for the efficacy of psychotherapies in cardiac patients is that their use is limited by the lack of mental health professionals with specialized training in cardiac psychology and limits on the financial resources needed to sustain clinically meaningful levels of intervention (269).

There are many types of effective psychotherapy (270). The American Psychiatric Association practice guidelines state that CBT and interpersonal psychotherapy (IPT) have the best-documented efficacy for treatment of MDD and anxiety disorders (271,272). Problem-solving therapy and relaxation therapies are also proven adjuncts to treatment for depression and anxiety, and in heart patients, emotionally focused therapy (EFT) for couples and families has been shown to improve cardiac outcomes (273).

There are many forms of CBT, all of which focus on changing distorted thought patterns that are driving harmful emotion and dysfunctional behavior, creating effective strategies for overcoming problems, generating self-efficacy and self-esteem, building the patient's internal locus of control, and reducing mental and biological stress (274,275).

IPT is an empirically validated treatment proven effective for clinical depression, social phobias, major anxiety disorder, bipolar disorder, and post-traumatic stress disorder (276,277). The focus of IPT is on how the patient experiences and resolves stressful life events (i.e., the death of a loved one, a conflict with a significant other, a stressful career change, or surgery). IPT is time-limited for the treatment of psychological disorders associated with acutely stressful events (weekly sessions for 12–16 weeks on average) or it may be maintained over time for patients with chronic problems and/or a long history of stressful life circumstances (i.e., a history of child abuse). The goal of IPT is to encourage appropriate expression/release of negative emotion (anger, fear, sadness), resolve interpersonal struggles, overcome interpersonal deficits, decrease social isolation, increase patient ability to assert his or her needs and wishes in interpersonal encounters, build patient self-esteem and confidence, and encourage taking appropriate risks (278). With IPT the therapist's stance is one of being the patient's supportive ally.

EFT for couples and families is a structured psychotherapy designed to repair distressed relationships and/or forge sound relationships where both partners feel close, safe, and nurtured and take better care of themselves (279). It has been studied extensively and proven effective with individuals and families experiencing chronic and acute stress and distress (280–282). Couple quality has been found to moderate the relationship between stress and wellness, acting as a protective factor in emotionally healthy couples, or increasing vulnerability to illness for at-risk patients who are in emotionally unhealthy relationships (283). Couple conflict has been associated with increased blood pressure (284) and high levels of catecholamines and stress hormones (285). Conversely, pre-MI marital happiness is consistently associated with lower levels of stress in patients following MI and better health outcomes (286).

In a study of social support and wives of CHD patients, quantitative aspects of social support (i.e., the number of people offering help) following MI were unrelated to subsequent emotional adjustment and utilization of healthcare services, however: qualitative aspects of support, such as satisfaction with support from children and partners, were closely associated with positive health outcomes (287). The psychological distress of each partner and the couple's adjustment in dealing with CHD plays a substantial role in patient recovery from significant cardiac events. Levels of psychological distress in *both* partner and patients have been identified

as significant, with 57% of patients and 40% of partners meeting criteria for a psychiatric disorder following a major cardiac event (288). Researchers have suggested that this is an expression of empathy: the more couples love and rely on one-another, the more they find a significant cardiac event stressful (289). A patient's wellbeing in their primary relationship has been found to be a powerful predictor of recovery from a cardiac event (290) and relationship problems that existed before a cardiac event have been shown to worsen after a cardiac episode (291).

Clinical hypnosis

Clinical hypnosis was first approved by the American Medical Association as a medical intervention in 1958 (292). The general public tends to confuse clinical hypnosis with stage hypnosis – an entertainment medium that uses mind control methods which are known to be harmful to the mind. Clinical hypnosis is starkly different from the entertainment medium, however. It uses well-researched mental relaxation and focusing procedures to help a patient concentrate on issues relating to their health and wellbeing. The patient is in control throughout the experience, is aware of everything, and remembers everything.

In cardiac psychology, our interest in clinical hypnosis stems from its ability to do two important things. First, it produces the relaxation response, the biological opposite of stress (293). The relaxation response has a well-documented set of healthful neuroendocrine and cardiovascular effects discussed in the next section. It also calms the mind and body for effective meditation, which renders yet another set of clinically proven benefits (see detail provided in the following section).

The second important benefit of clinical hypnosis is its ability to decouple cognitive control between frontal cortex conflict monitoring functions and limbic brain functions of memory and emotion (294). As a result, the patient is able to gain better access to his or her subconscious memories, thoughts, and feelings. Patient distress, depression, and anxiety often stem from difficult experiences in the past and their unresolved emotional legacy, most of which is stored in the subconscious. Subconscious emotional distress then fuels a low-grade, chronic cycle of SNS hyperactivity. Hypnosis is a rapid way to allow patient access to subconscious memory and experience cathartic levels of release from old emotional pain, as well as gain greater insight and willpower relating to health and healthy behaviors.

Meditation

Just as stress research taught us how stress builds an unhealthy brain, meditation research is showing us how to build a healthy brain and body. Dr. Herb Benson's pioneering research in the 70s showed that 20 minutes or more of daily meditation invokes the human relaxation response, a return to parasympathetic tone, which immediately lowers blood pressure, improves circulation to the heart and vital organs, stabilizes heart rate, slows and deepens breathing, relaxes the musculoskeletal system, reduces inflammation, and increases mental clarity and peace of mind (295). Dr. Jon Kabat-Zinn's work confirmed these findings. Mention has already been made of studies by Manchanda and Gupta, showing that meditation in combination with a heart-healthy yogic lifestyle reverses atherosclerosis in patients with metabolic syndrome and CAD (296,297).

It also appears that meditation induces positive changes in inflammatory gene expression in expert meditators (298). In experienced meditators, it also regulates gene expression profiling in circulating immune cells, which supports the hypothesis that yogic/meditative practices have a measurable effect at the molecular level (299).

Meditation also has remarkable effects on the mind, the brain, and the neuroendocrine system. A 2013 systematic review and meta-analysis of 47 research trials involving 3,515 participants found that mindfulness meditation for 8 weeks had a positive clinical effect on mild to moderate anxiety, depression, and physical pain (300). A 2014 meta-analysis which reviewed 21 neuroimaging studies found that there are 8 brain regions consistently altered in advanced meditators "including areas key to meta-awareness (frontopolar cortex/BA 10), exteroceptive and interoceptive body awareness (sensory cortices and insula), memory consolidation and reconsolidation (hippocampus), self- and emotional regulation (anterior and mid cingulate; orbitofrontal cortex), and intra- and interhemispheric communication (superior longitudinal fasciculus; corpus callosum)" (301).Yale University, using FMRI, studied experienced and novice meditators as they practiced three different meditation techniques and found that experienced meditators had decreased activity in areas of the brain called "the default mode network" which, when overactive, is responsible for

ruminative "me-centered" stressful thinking, lapses of attention, disorders like anxiety, and the build-up of plaque in Alzheimers (302). The default mode network consists of the medial prefrontal and posterior cingulate cortex (emotion and memory link, internally directed cognition, and attention). FMRI scans from this study showed that when the default mode network was less active, brain regions associated with self-monitoring and cognitive control were coactivated in experienced meditators but not novices. This indicates that experienced meditators are constantly monitoring and suppressing negative "me" thoughts (the mind-wandering associated with mental distress, depression, and anxiety). Meditators did this both during meditation and also when just resting.

Lazar *et al*. found that meditation causes the right side of the frontal brain cortex to thicken – an area of the brain related to somatosensory processing (body awareness and control), auditory processing, visual processing, and interoceptive processing (mindfulness and awareness) (303). The conclusion of this study was that meditators show increased neuroplasticity, integration of senses and emotion, higher levels of attention and awareness, and reversal of age-related thinning of the frontal cortex.

Holzel *et al*. found that mindfulness meditation for just 8 weeks induces positive, identifiable changes in gray matter within the left hippocampus, the posterior cingulate cortex, the temporoparietal junction, and the cerebellum (304). These areas of the brain correlate (respectively) with memory and spatial navigation, emotions related to significant personal memories, integration of internal and external information and self–other distinctions, coordination, motor control, cognitive functions like language and attention, and regulating fear and pleasure responses. A National Academy of Sciences study, using diffusion tensor imaging, showed that mindfulness meditators demonstrate improved white-matter neuroplasticity in the anterior cingulate cortex, a part of the brain network related to self-regulation of thought, attention, and mood (305).

Clearly, meditation is effective for the prevention of heart disease and other stress-related disorders of the brain and body, including distress, depression, and anxiety. It is also an effective treatment modality for these problems, except in cases of moderate to severe depression and anxiety. The challenge with meditation as a clinical modality is its low rate of patient compliance. A calm mind and body are necessary for effective meditation. Most people new to its practice get frustrated trying to calm their minds and bodies and give up on meditating before they derive any clinical benefits. To sidestep this difficulty, this author developed hypnotic meditation: a short series of progressive relaxation procedures that precede a scientifically validated meditation practice. Hypnotic meditation allows the user to relax their mind and body quickly and easily so they can slide deep into meditation and enjoy its benefits right away.

Exercise and somatic relaxation techniques

Exercise is known to be essential to cardiovascular health (306). When exercise is combined with proven stress reduction techniques like simple yoga or stretching exercises, it is been shown to improve cardiovascular health and cardiovascular outcomes in people who already have CAD (307). Exercise therapy plus antidepressant medication used together have been shown to reduce the risk of cardiovascular events in patients with major depression (308). Evidence also suggests that relaxation and breathing therapies are effective in reducing exhaustion in CAD patients and may help prevent recurrent MI and clinical restenosis following coronary angioplasty (309,310).

Support groups

Patient support groups provide social support in a safe, nonjudgmental environment, reduce anxiety, help patients learn how to effectively identify and report symptoms to their physicians, and increase rates of patient compliance with physician's orders (311).

Cardiac rehabilitation

According to the American Heart Association, "cardiac rehabilitation" refers to a multicomponent and coordinated intervention aimed at optimizing the cardiac patient's physical, psychological, and social functioning and reducing morbidity and mortality (312). Cardiac rehabilitation programs usually focus on therapy (cardiac, respiratory, physical, and occupational), diet and lifestyle education, and enhancing patient compliance with physician's orders. Cardiac rehabilitation programs that include psychosocial education and group counseling and support are rarer, but have been shown to reduce patient distress, treat mild depression and anxiety, improve patient compliance with physician instructions, and improve prognosis in coronary heart disease (313).

Case management

Case management of cardiac patients is well-known to increase compliance with physician instructions and improve cardiac outcomes, and the need for case management is even greater for cardiac patients who suffer from distress, depression, and anxiety (314). A number of novel methods for case-managing patients with regular contact and follow up, including computer-based technology, have been conceived. In one recent study, "usual care" case management (serial notification of patient status to primary medical providers) was compared to a novel telephone-based low-intensity multicomponent coordinated care (CC) intervention using a social work manager to coordinate assessment and stepped care of psychiatric conditions and provide support as appropriate. Patients were high-risk cardiac inpatients (acute coronary syndrome, arrhythmia, or heart failure) found to have clinical depression, GAD, or panic disorder on structured assessment, who were randomly assigned to either of the two groups. At 24 weeks patients who received CC had significant improvements in symptoms of depression and anxiety, better general functioning, higher rates of physician compliance, and higher rates of treatment for their mental health disorder than patients in the control group (315).

Implications

Hundreds of studies in this area have derived the same conclusion: anxiety and depression at clinical and subclinical levels are common among cardiac patients and contribute substantially to disease etiology and patient morbidity and mortality.

In India, rising rates of chronic stress, depression, and anxiety in the general population will serve to sustain high prevalence rates for cardiovascular disease and impair the medical establishment's ability to respond to what many doctors have termed "India's heart health crisis."

The imperative in cardiac settings is to recognize distress, depression, and anxiety in heart patients as early as possible and treat these problems effectively to increase rates of recovery from heart disease, decrease patient risk of subsequent cardiac events, boost patient functioning and coping skills, improve patient lifestyle choices, and increase patient adherence with physician's orders.

There are effective treatments for heart patients with psychiatric issues, but due to lack of qualified doctoral-level clinicians in mental health and cardiac psychology in India, effective assessment and treatment of mental disorders among cardiac patients remains elusive. The cost of providing treatment and the stigma associated with mental illness in India are also confounding factors in attempts to intervene effectively with this population.

The author, having recently released a heart patient self-help manual on stress, depression, and anxiety, strongly encourages clinicians and researchers in India to focus now on developing new, innovative, cost-effective, culturally sensitive means for treating distress, depression, and anxiety in patients with cardiovascular disease. More emphasis in higher education and more resources are needed to train a cadre of doctoral-level mental health professionals. Further, it is suggested that cardiology takes the lead role in promoting primary prevention programs that elucidate the nature of stress and its consequences, destigmatize stress-related mental problems, and disseminate evidence-based practices that can prevent the progression of chronic stress to heart disease, depression, and anxiety.

India's spiritual legacy to the world – the yogic diet and lifestyle, with its emphasis on regular meditation – has been proven to improve cardiovascular health in patients with CVD, stop stress in its tracks, reduce the symptoms of mild to moderate depression and anxiety, and prevent stress-related illnesses. A revival of the yogic lifestyle is, in this author's opinion, the best way to avert an escalation of the heart-health crisis in India. The key to success rests in making yoga newly relevant to a youthful populace largely focused on increasing its standard of living.

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