

Editorial

Depression, migraine, and cardiovascular disease: Sadness really can break your heart

Background

Depression increases the risk of cardiovascular disease (CVD) by 1.5 to 2 times in healthy individuals, and depression in CVD patients increases the risk for cardiac morbidity and mortality by 1.5 to 2.5 times [1–7]. Psychosocial stressors (although not specific to depression) are also associated with significantly increased risk of myocardial infarction (MI) almost roughly equivalent to the risks associated with smoking and diabetes and higher than the risk of obesity [8]. Conversely, in a metaanalysis of 25 studies with 106,628 subjects, the relative risk of dying (all causes) in depressed subjects was 1.81 (95% CI, 1.58–2.07) compared with age- and sex-matched nondepressed control subjects [9] with a risk of 1.5 (95% CI, 1.4–1.6) for men and 1.7 (95% CI, 1.7–1.8) for women of dying from CVD [10]. Attempts to explain the nature of the stress/depression–CVD association have resulted in conflicting results [11] as the impact of such comorbidities goes beyond the disability resulting from the presence of more than one disease to impairing quality and shortening span of life.

Migraine and depression are also known to co-occur, and most studies suggest that the frequency of this phenomenon is greater than can be explained by chance [12]. The presence of either migraine or depression is a risk factor for the other condition [13]. Migraine also increases the risk for CVD [14,15], especially migraine with aura, which also has the highest comorbidity with depression [16]. Migraine–depression–CVD tend to cluster in susceptible individuals with poorer health outcomes. Hung et al [17] (this issue) found the presence of migraine in patients with depression acted as an independent contributor to poorer quality of life as measured by health-related quality of life tool. This study clearly demonstrates that the presence of migraine worsened the impact on patients' health and quality of life compared with the presence of depression alone [17]. Given that depression already accounts for 12% of the total disability-adjusted life-years [18] and is projected to be the second leading cause of disease burden for developed countries by 2020 [19], conditions that worsen the impact of this illness on function clearly need to be recognized and treated.

Given the negative impact of depression on the course of CVD, it is important to identify patients with CVD who are at risk for depression. Several screening tools have been used, and most have some advantages as well as limitations. The Beck Depression Inventory (BDI) is a widely used self-rating questionnaire to identify depressive symptoms and severity [20] in psychiatric and nonpsychiatric populations. Since depressive symptoms also include multiple somatic complaints such as tiredness, insomnia, change in appetite, and lack of concentration that can also be part of a general medical condition such as CVD, the BDI use in medical patients was questioned as a positive score may reflect the somatic concerns rather than depressive symptoms. Thombs et al. [21] (this issue) addressed such concern. The authors studied depressive symptoms in 477 hospitalized patients with recent MI by using the BDI revised version (BDI-II). The study aimed to confirm a factor model for the BDI-II that would allow for finding the best-fitted model for depressive symptoms in cardiac patients following adjusting for somatic symptoms overlap. Depressive symptoms occurred in 22.4% of post-MI patients in keeping with previous reports of depression prevalence in CVD patients [5]. The study found that somatic symptoms accounted for only 11% of the variance, and the best-fitting model included the general depression, somatic, and cognitive factors model [21]. Although the BDI is not diagnostic of depression and contains several somatic factors, this study demonstrated a new approach to using the BDI to identify depressive symptoms in cardiac patients despite the presence of somatic concerns.

Similarly, Wang et al [22] (this issue) found depressive symptoms to occur in about one in five Chinese cardiac patients ($n=200$) using the Chinese version of the Cardiac Depression Scale (CDS) [23]. The CDS has a high correlation with the BDI (0.73) and a correlation of 0.67 with the clinical assessment of depression [23], making it another useful self-administered screening tool for depressive symptoms in cardiac patients. With the exception of one item from the original CDS (item 26, relating to sexual activity), the Chinese translation of the CDS showed acceptable internal consistency and test–retest reliability.

Interestingly, these studies [21,22] (this issue) found similar prevalence rates of depression in cardiac patients despite the use of different screening tools in different populations (95% North American Caucasian and 100% Chinese, respectively).

Another marker that may prove useful as a predictor for mortality from CVD is cognitive ability. In a naturalistic cohort study of 6424 individuals, Shipley et al. [24] (this issue) found a significant association between slower reaction time, as a measure of information processing efficiency that is less influenced by educational and socioeconomic background, and mortality from CVD. Cognitive impairment has also been reported to occur in depression [25] and migraine [26], but it is unknown if this is associated with excess mortality from CVD. It will be of interest to assess cognitive function in patients with CVD adjusting for the comorbidity with either migraine or depression or both.

Despite the consistent findings of association between depression and CVD, the factors mediating this association remain to be confirmed. A number of hypotheses about the pathophysiological mechanisms linking depression to CVD have been proposed. Depression has been linked to diminished heart rate variability [27], for example, which may increase vulnerability to cardiac events [28]. Inflammatory markers and hypercortisolemia have also been proposed as mediators of depression in CVD [11]. Dysregulation of the hypothalamic–pituitary–adrenal axis (HPA) is a reliable finding in patients with depression [29], and it is likely that early sensitization of HPA axis in response to stress may also lead to excess circulating catecholamines leading to vasoconstriction, tachycardia, and platelets activity modulation contributing to the development of migraine and CVD. Migraine was widely considered to be a vascular phenomenon following the observation that the vasodilatation occurring during a migraine attack was relieved by the administration of a

vasoconstrictor such as ergotamine [30]. In an attempt to explain the role of cortisol in this complex cascade of events linking depression and CVD, Bhattacharyya et al. [31] (this issue) investigated the cortisol level and depressed mood using the BDI in 88 patients undergoing investigations for CVD. The authors noticed significant flattening of the cortisol rhythm in depressed CVD patients compared with depressed non-CVD patients. Although the sample size in each group is modest and the measure of depression on the BDI is subclinical, this study highlights an interesting pathophysiological phenomenon that may be used as biological marker for future studies. It is likely that depression, CVD, and migraine are linked by pathophysiological pathways that have their origins in fetal programming, especially in epigenetic processes that, in the presence of the triggering factors such as the hormonal milieu, inflammation, and the suitable environmental potentials, both internal and external, such as chronic stress, significant life events, dietary habits, and life style, may produce one or all of these phenotypes (Fig. 1).

Treatment of these conditions as a strategy to reduce the burden of a comorbid condition has proven to be complex for these illnesses. Many of the medications used to treat migraine can only be carefully combined with antidepressant medications. Some antidepressants appear to have good effect at modulating pain but are not generally effective against acute migraine. Accepting that depression/migraine and CVDs are highly comorbid and depression predicts poorer prognosis for CVD, it is a reasonable hypothesis that treating depression in patients with CVD will improve outcome. Unfortunately, however, large-scale investigations examining the impact of treating depression in CVD patients [32] have struggled to demonstrate improvement in cardiac disease outcomes in patients receiving pharmacological or nonpharmacological treatment for depression. Although patients in the ENRICHD trial showed improvement in depression, the mortality rate in the depression-treated and depression-untreated group was similar ($\approx 24\%$). A follow-up (after 6 months) study of the ENRICHD trial did show that patients who were refractory to depression treatment were at higher risk of mortality [33], supporting the importance of not just treatment but also *successful* treatment of depression in CVD patients. Psychotherapy may reduce mortality in CVD patients if initiated within 2 months following the cardiac event [34]. Further studies showed a significant correlation between nonresponse to antidepressant treatment and subsequent cardiac events [35]. Although a study of sertraline in patients with depression postacute coronary event (the SADHART trial) showed a significant correlation between sertraline administration and surrogate end points such as reduced platelets activity and endothelial biomarkers, no significant clinical advantages were reported for cardiac and mortality outcomes for treated and untreated patients [36]. Although it appears reasonable that intervening to treat comorbid conditions that worsen impact in patients with CVD should improve outcome, there appear to be

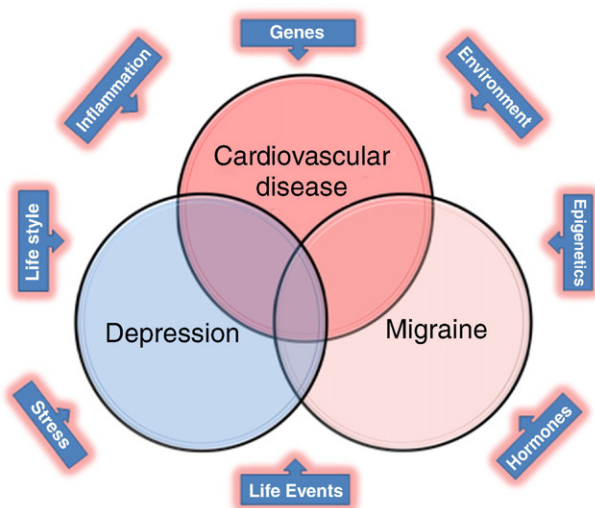


Fig. 1. Schematic representation of the depression–migraine–CVD association.

complex relations between treatment and factors that actually reduce mortality following an acute cardiac event.

Summary

Depression, migraine, and CVD are common disorders with a major impact on personal and social function and a major financial cost to society. These illnesses are highly comorbid, and there are multiple proposed pathways to account for these associations, none of which have been proven as causative factors in the associations between these conditions. Nonetheless, patients with CVD should be screened for depression, and the articles described in this issue extend the range of tools that are available for that purpose. Similarly, patients with depression need to be assessed for the presence of migraine, which can exert an independent and negative effect on function, as indicated by Hung et al. in this issue. Patients with depression and/or migraine also need monitoring for the emergence of CVD as either of these conditions elevate for risk of CVD, and the combination may elevate risk further than either condition alone.

The articles reviewed for this issue, while very different in their foci, all highlight the need for further integration between psychiatric and medical specialists. Comprehensive care of patients with any of these conditions cannot be provided without attending to the psychiatric and somatic needs of the patients, and in the hospital setting, this requires clinical teams that are multidisciplinary and comfortable across traditional boundaries of care. In primary care, it requires clinicians to be vigilant for the emergence of symptoms that signal that patients' distress may be best understood under a different label, with the different treatment strategies implied by this. Investigators such as Thombs, Wang, Shipley, and their colleagues are providing tools that are reasonable for routine clinical use. Communicating the information that studies such as theirs provide so that there is uptake of such tools in real world settings remains a challenge for all involved in educating the next generation of clinicians in both primary and specialty care.

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