Heart Disease and Depression

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Depression is common in patients with physical illness. The National Center of Neurology and Psychiatry has launched a joint project with five other centers in Japan, aiming at improving the quality of mental care in patients with physical illness. In the present overview focusing on heart disease, we review the prevalence of depression in patients with heart disease, the impact of depression on cardiac prognosis, the possible mechanisms of depression in patients with heart disease, drug-drug interactions between cardiac and psychotropic agents and the possible therapeutic approaches to treating these patients. Depression and heart disease often coexist and each can lead to the other. Various biological and behavioral mechanisms have been proposed to explain an association between heart disease and depression, including autonomic nervous system activity, impairment of platelet function, endothelial dysfunction, inflammatory changes, and health-related behaviors. Combination therapy with tricyclic antidepressant and cardiac agents must be approached with caution to avoid drug-drug interactions. Selective serotonin reuptake inhibitors (SSRIs) are the first line treatment for patients with heart disease and moderate to severe depression. Although no single intervention has been established as the standardized treatment, recent studies suggest that collaborative care improves both depressive symptoms and cardiac outcomes, and that patient’s participation is a key to successful treatment. Bridging the gap between cardiology and psychiatry is essential, and psychiatrists can play a vital role in taking care of the mental health of patients with heart disease.

Key words: depression, heart disease, antidepressant, collaborative care

Introduction

Depression is a subject of growing importance in patients with physical illness. The prevalence of depression varies according to the definition and assessment methods. In general, the prevalence of depression is 13%-20% in patients with cancer [1], 29%-36% with stroke [2], 20% with coronary heart disease [3], and 11% with diabetes mellitus patients [4]. Negative impacts of depression on the outcomes of patients with phys-
ical illness are well-known. Depression may raise the mortality risk of patients with cancer 1.25-fold [5] and double the risk in those with myocardial infarction [6], while depression increases the length of stay in hospitalization and clinic visits in patients with stroke [7]. Also, depression may reduce glycemic control [8] and adherence to treatment in patients with diabetes mellitus [9].

To improve the quality of mental health care in patients with physical illness, the National Center of Neurology and Psychiatry (NCNP) has launched a joint project with five other national centers in Japan, including the National Cancer Center (cancer), the National Cerebral and Cardiovascular Center (stroke and heart disease), the National Center for Global Health and Medicine (diabetes mellitus), the National Center for Geriatrics and Gerontology (dementia), and the National Center for Child Health and Development (chronic inflammatory bowel disease). The project is aimed at promoting (A) training of health care providers in medical fields, (B) certification of model institutions and communities to provide high quality of mental health care for patients with physical illness, and (C) clinical research on the effectiveness of collaborative care programs and a support network to facilitate the integration of mental health care into general health care.

In the present overview, we are focusing on heart disease, and we review the prevalence of depression in patients with heart disease, the impact of depression on cardiac outcomes, the possible mechanisms of depression in patients with heart disease, drug-drug interactions between cardiac and psychotropic agents, and the possible therapeutic approaches to treating these patients.

### Prevalence of Depression and its Impact on Cardiac Outcomes

There is a growing body of literature on an association between heart disease and depression. “Heart disease” is a broad term to describe a range of diseases in the heart, including coronary heart disease or coronary artery disease, heart attack, and heart failure. The result of a meta-analysis shows that 20% of patients with coronary heart disease or coronary artery disease have depression [3]. The results of follow-up community-based study over the past decade show moderate to strong relationships between depression and heart disease such as angina and myocardial infarction [10]. A Swedish twin study in 2009 suggested that heart disease increases the incidence of depression risk 2.8-fold times (95%CI: 1.9-4.2), while depression increases the incidence of cardiovascular disease 2.5-fold times (95%CI: 1.7-3.8) [11]. Patients with heart disease are prone to depression, while depression can lead to heart disease.

Both depression and heart disease are leading causes of disability [12]. The impact of comorbidity of those two diseases has been highlighted in a landmark study demonstrating that the risk of cardiac death in the 6 months after acute myocardial infarction is about 4 times greater in patients with depression compared to those without [13]. The publication of this study in 1993 stimulated further research to determine the impact of depression on cardiac outcomes [10]. Now, depression is known as a predictive factor of poor outcomes after myocardial infarction, including recurrence, cardiac death and all causes of death. Depression increases mortality 2.3-fold times after myocardial infarction [14], 1.8-fold times in congestive heart failure [15], 3.3-fold...
times in unstable angina [16], and 2.4-fold times after coronary artery bypass [17]. A Japanese study comparing depression, anxiety, and anger reports that depression in hospitalized cardiovascular patients is a stronger independent risk factor for adverse cardiac events than either anxiety or anger [18]. In addition to the health risks, the co-morbid condition is costly, imposing high out-of-pocket burdens on these patients. The out-of-pocket expenditure burden is estimated to double in patients who suffer from both heart disease and psychological distress compared to that in patients with heart disease only [19].

Possible Mechanisms of the Link between Heart Disease and Depression

Many mechanisms have been proposed to explain the link between heart disease and depression from basic science to the epidemiological level. Many studies have suggested that biological, psychosocial, and behavioral factors are related to the association between heart disease and depression [20]. Although the mechanism underlying this relationship remains not fully understood, these efforts help generate possible intervention strategies.

Biological factors

Biological factors representing a possible link between heart disease and depression include (A) neuroendocrine dysregulation, (B) inflammation, and (C) enhanced platelet activation and endothelial dysfunction. In addition to its effects during the acute phase of heart disease, prolonged stress activates the hypothalamic-pituitary-adrenal (HPA) axis and releases cortisol. High levels of cortisol deplete collagen, counteract insulin, decrease bone density and weaken the immune system, often resulting in various health conditions and diseases. On the other hand, a strong association exists between depression and increased cortisol. A previous study revealed that highly stressed women with cardiovascular disease have a 1.6-fold greater risk (95% CI: 1.3-2.2) compared to those without stress [21].

Meta analyses suggest that inflammation may also be a link between heart disease and depression. Depression and C-reactive protein (CRP), interleukin (IL)-1, and IL-6 are positively associated in both clinical and community populations [22]. CRP concentration is related to risks of coronary heart disease, ischemic stroke, and vascular mortality [23].

Platelet activation and endothelial dysfunction are other possible biological mechanisms that connect heart disease with depression. Depression increase susceptibility to blood clotting due to alterations in multiple steps of the clotting cascade, including platelet activation and aggregation [24]. D-dimer, von Willebrand factor and plasminogen activator inhibitor (PAI) levels are related to depression [25]. It is worth noting that treatment with sertraline in depressed patients after acute coronary syndrome is associated with reduced platelet/endothelial activation despite coadministration of antiplatelet regimens such as aspirin [26].

A decrease in nitric oxide (NO) availability would predispose patients to developing atherosclerosis [20]. The levels of both plasma NO metabolite (NOx) and platelet endothelial NO synthase (eNOS) activity are significantly lower in patients with major depression compared with healthy control subjects [27]. These results suggest that patients with depression are at risk for atherosclerosis; however, treatment with a serotonin and norepinephrine reuptake inhibitor (SNRI) (milnacipran) significantly increases the plasma NOx levels [28].
Another interesting topic is brain-derived neurotrophic factor (BDNF). There is a strong evidence that serum BDNF levels are abnormally low in patients with major depressive disorder and that the BDNF levels are elevated with antidepressant treatment [29]. BDNF also plays an important role in atherogenesis and plaque instability [30].

**Psychosocial factors**

The medical community has accepted that acute myocardial infarction and sudden cardiac death can be triggered by stressors such as heavy physical exertion and severe emotional stress [31], and the meta-analysis shows that depression is as a strong predictor of coronary heart disease [32]. The INTERHERT study, a large global standardized case control study, involving a sample of 24,767 patients in 52 countries, revealed that the presence of psychosocial stressors is associated with increased risk of acute myocardial infarction. The psychosocial stressors are ongoing work-related stress, ongoing home stress, ongoing general stress and financial stress [33]. The effect of psychosocial factors on cardiac function is likely greater than is commonly recognized, resulting in an increasing level of interest in this area.

An increased incidence of acute cardiac events has been reported in communities after stressful events. After the Great Hanshin Earthquake in Japan [34], increased numbers of patients were admitted to emergency departments due to myocardial infarction, and cardiovascular events increased among German supporters during the World Cup match [35]. These consequences clearly show the potential for acute and direct impacts of life events on the human autonomic nervous system.

Since the theory that “Type A” personality, that is, a compound of hostility, competitiveness and impatience, triggers heart attacks, was introduced in the United States in the late 1950s, the personality theory remained highly controversial in the scientific community. Although researchers in recent years have tended to deny any association between heart disease and personality, related constructs to those of the Type A personality are regaining attention. A systematic review in 2009 showed that anger and hostility increased risk of cardiovascular disease [36]. Recently, a new type of personality trait, the Type D, was found to increase the risk of cardiovascular events. The Type D personality was also linked to an increased risk of depression [37]. Biological and behavioral pathways are being studied to explain these adverse effects of the Type D personality on health.

**Behavioral factors**

Health risk behaviors including smoking, unhealthy diet, and physical inactivity contribute to risk factors of heart disease. These behavioral factors are also prevalent in patients with depression, including smoking [38], and lower levels of physical and social activities [39]. Nonadherence to medication is a risk factor for both adverse outcomes of depression and coronary heart disease [40].

**Genetic determinants**

Genetic connection is a new avenue of investigation to explain the link between heart disease and depression. An American study of 2,731 male-male twin pairs from the Vietnam Era Twin Registry suggests that 20% of genetic influence is common across heart disease and depression [41]. The Swedish population-based twin registry with 30,374 twins also shows the possibility of genetic factors to explain the relationship between major depression and coronary heart disease [11]. The serotonin transporter gene
(5-HTTLPR) polymorphism is related to both emotion and platelet activation and is, therefore, a promising candidate as a genetic determinant of linked heart disease and depression [20]. Carriers of the s allele of 5-HTTLPR are considered to be more vulnerable to depression in patients with heart disease [42].

**Therapeutic Approaches**

**Medications**

Treatment options for depression include antidepressants, cognitive behavioral therapy, and physical activity. The American Heart Association (AHA) recommends SSRI or SNRI as the first-line treatment for moderate to severe depression [43]. There is strong evidence of the safety of the SSRI, sertraline in particular. Sertraline has shown no significant adverse effects in patients with coronary heart disease in the Sertraline Antidepressant Heart Attack Randomized Trial [44]. Citalopram was also recommended as a first-line agent based on a randomized trial; however, in 2012, the US Food and Drug Administration has warned of drug-induced QTc interval prolongation and *torsade de pointes* when using citalopram at doses greater than 40 mg per day (http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm).

One of the challenges to treating depression in patients with heart disease is that cardiologists must decide whether to use antidepressants as primary treatment. In fact, depression in patients with heart disease is often left untreated, or the best treatment is often not provided. It is also true in reality that there are various barriers to coordinating with the liaison consultation psychiatrist in clinical settings. Even though the cardiologist consults with the psychiatrist, advice from the psychiatrist is often limited to advocating for the temporary discontinuation of psychotropic agents.

New cardiac and psychotropic agents are constantly being introduced into practice. Although the safety of each drug is assessed, every possible combination with other drugs cannot be evaluated. In addition, polypharmacy is common in psychiatric patients as well as in elderly patients, while cardiologists and primary care physicians have more opportunities to prescribe psychotropic medications for comorbid patients. These trends increase the potential risk of drug-drug interaction, but no consensus exists regarding cardiac drug interactions with concurrent psychotropic prescriptions. Strain et al. conducted a series of studies on the drug combinations among cardiologists, psychiatrists and experts in clinical pharmacology since the 1990s [45-47]. They systematically reviewed commonly prescribed cardiac and psychotropic medications, and rated the level of significance in interaction between cardiac drugs and psychotropic drugs as “major” (potentially life-threatening or capable of causing permanent death), “moderate” (a deterioration in a patient’s status, resulting in additional treatment or hospitalization or extension of hospital stay), or “minor” (bothersome or unnoticeable) [45, 47]. In 2002, the review was updated with newly added drugs [47].

Table 1 shows 15 drug combinations that would increase the risk of serious adverse events. Five of the 15 combinations include tricyclic antidepressants. Combination therapy with tricyclic antidepressants may cause fatal ventricular arrhythmia, *torsade de pointes*, due to prolongation of QT interval with ibutilide, and interference with brethyllium’s effects, and may potentiate the pressure effects of direct acting sympathomimetics (e.g., dobutamine, norepinephrine, epinephrine, and phenylephrine) while decreasing the pressor response to indirect-acting sympathomimetics (e.g., dopamine) [45]. Tricyclic antidepres-
Table 1. Major drug-drug interactions between cardiac and psychotropic agents

<table>
<thead>
<tr>
<th>Cardiac agents</th>
<th>Psychotropic agents</th>
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<tbody>
<tr>
<td>Adenosine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Nefazodone</td>
</tr>
<tr>
<td>Bretylium</td>
<td>Tricyclic antidepressants (desipramine, doxepin, imipramine)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Lithium</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Phenothiazines/Haloperidol</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Sympathomimetics (dobutamine, dopamine, amphetamines, ephedrine, phenylephrine)</td>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>Sympathomimetics (dobutamine, norepinephrine, epinephrine, phenylephrine)</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Barbiturates</td>
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</tbody>
</table>

This table is a summary of the 1999 [45] and 2002 [47] studies by Strain et al.

SSRIs are generally safe, but combining them with furosemid or quinidine requires caution. When furosemid and fluoxetine are co-administered, there is a risk of hyponatremia. Concurrent use of quinidine and an SSRI inhibits metabolic enzyme, and thus the plasma concentration and side effects of both agents should be observed. Drug-drug interactions newly added in 2002 include atorvastatin and nefazodone, and warfarin and barbiturates. Because both combinations affect the metabolism of cardiac agents, plasma concentrations of atorvastatin and warfarin should be observed [47]. The data are still limited, and so the risks and benefits of psychotropic agents should be carefully balanced, and potential drug-drug interactions should be closely monitored. Good quality studies are needed to establish standard medication protocols in comorbid patients with depression and heart disease.

**Cognitive behavioral therapy**

The Harvard research group conducted a large multicenter randomized controlled trial, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study in 2,481 patients with myocardial infarction receiving treatment for depression with cognitive behavioral therapy and SSRIs. The intervention has not been found to reduce cardiovascular events or mortality, although depression and social isolation are improved [49]. Since that study appeared, no large-scale clinical trial has
been conducted regarding cognitive behavioral therapy in patients with heart disease. A post hoc subgroup analysis of ENRICHD during the 29-month follow-up period has revealed a significant reduction in mortality and morbidity in depressed post-myocardial infarction patients receiving SSRIs [50].

**Physical activity**

The potential benefits of exercise for improving cardiovascular fitness [51] and reducing depressive symptoms [52] have been emphasized in recent studies. Since depression may be a barrier to participating in exercise programs, health care providers should facilitate patient participation in exercise programs tailored to patients’ cardiac conditions.

**Collaborative care**

The results of two studies published in 2010 deserve attention. One described patient-centered management based on guidelines provided by nurses for patients with depression and chronic disease that has shown to improve both depression and chronic disease [53], and the other described collaborative care (“enhanced depression care”) for patients with coronary syndrome that has shown to improve depression and cardiac prognosis with a high level of patient satisfaction [54].

Katon et al. conducted a single-blind, randomized, controlled trial in 14 primary care clinics to examine depression management and improvement of glycemic/hypertension/lipid control in 214 participants with poorly controlled diabetes mellitus, coronary heart disease, or both and coexisting depression [53]. The 12-month intervention included self-care support and medication for depression, hyperglycemia, hypertension, and hyperlipidemia. The target goal was determined among the patient, nurse, and the primary care physician. The nurse coordinated care between the primary care physician and a psychiatrist, and played a central role in intervention. The patient visited the clinic 2 or 3 times a week, while the nurse supervised the patient weekly.

Collaborative care is an established program in primary care [55]. It consists of: (A) an enhanced care approach, with treatment delivered by a clinical nurse specialist, psychologist, social worker, and/or psychiatrist; (B) the patient’s choice of psychotherapy and/or pharmacotherapy; (C) problem-solving therapy (psychotherapy); (D) a stepped-care approach with reviews of symptom severity and treatment; and (E) a standardized instrument used to track depressive symptoms. Davidson et al. applied this approach to patients with coronary syndrome [54].

In contrast to Berkman et al. who conducted a cross-sectional study in patients with major depression or minor depression [49], Davidson et al. limited the participants in their study to those with persistent depressive symptoms (a Beck Depression Scale score being greater than 10 for more than 3 months). It was a successful strategy to have a specific target population.

In the United Kingdom, the National Institute of Clinical Excellence (NICE) recommends a stepped care model for the treatment of depression [56]. Stepped care provides a framework for the care of patients with chronic illnesses, including hypertension, diabetes mellitus, and depression with the least costly, least intensive, and least restrictive treatment. The care is tailored based on severity, clinical status, and patient preference. The least intensive care includes self-care support, and care can be intensified to cognitive behavioral therapy, medication management, and hospital care (Table 2).
Patient Participation

According to a systematic review, no single intervention has been found to be effective for reducing 30-day rehospitalization in patients with chronic disease; but discharge planning, follow-up telephone call, and patient-centered discharge instructions have shown promising results in combined intervention [57]. Another systematic review found that case management and collaborative care (telephone and in person) can improve medication adherence for more than one condition, particularly in patients with depression [58]. This evidence suggests that patients’ views are essential for effective interventions. An interesting systematic review supports that the detection of depression during physical illness must take into account the patients’ beliefs and the integration of depression management with management for risk factors for cardiovascular disease [59].

Psychiatric liaison-consultation should be established in the department of cardiology, and training of coordinators who work between cardiologist and psychiatrist is needed for enhanced patient care.

Conclusion

There is a growing interest in the connection between heart disease and depression. Despite the extensive studies of this subject, much remains inconclusive because the association is complex and multifaceted. Depression in patients with heart disease is often overlooked and remains untreated. As health care becomes more specialized and fragmented, these comorbid patients are increasingly at risk to receive suboptimal care. Bridging the gap between cardiology and psychiatry is essential. Psychiatrists can play a vital role in improving mental health of patients with heart disease.

Table 2. Stepped care*

<table>
<thead>
<tr>
<th>Step</th>
<th>Targets</th>
<th>Treatments (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>All known and suspected presentations of depression</td>
<td>Assessment, support, psycho-education, active monitoring</td>
</tr>
<tr>
<td>Step 2</td>
<td>Persistent sub-threshold depressive symptoms; mild to moderate depression</td>
<td>Step 1 plus Low-intensity psychosocial interventions, psychological interventions, medication</td>
</tr>
<tr>
<td>Step 3</td>
<td>Persistent sub-threshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression</td>
<td>Step 2 plus high-intensity psychological interventions, combined treatments, collaborative care</td>
</tr>
<tr>
<td>Step 4</td>
<td>Severe and complex depression; risk to life; severe self-neglect</td>
<td>Step 3 plus, electroconvulsive therapy, crisis service, combined treatments, multi-professional and inpatient care</td>
</tr>
</tbody>
</table>

References


22. Howren MB, Lamkin DM, Suls J: Associations of


