WHAT IS THE ROLE OF NON-PHARMACOTHERAPY IN THE TREATMENT OF DEPRESSION WITH CARDIOVASCULAR DISEASE?

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Approval of The Dissertation

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Abstract

Depression and cardiovascular disease are two of the leading causes of disability and death in the U.S. and worldwide, respectively. Both health disparities are frequently managed and treated with conventional medicine using drugs that may increase the pain and suffering of patients due to unwanted side-effects, thereby likely prompting patient nonadherence to physician guidance and pharmaceutical interventions. This study aims to determine the effects of various non-pharmaceutical therapies including psychotherapy, exercise therapy, meditation, and acupuncture with musical therapy, and their influence on depression and cardiovascular disease. The main question in this review asks: do non-pharmaceutical therapies have positive effects on depression and cardiovascular disease? The results indicate that several non-pharmaceutical interventions do have positive effects on depression and cardiovascular disease, and can even be as effective as antidepressants for the treatment of depression, when used alone or in combination with conventional medical practices. While the current research on non-pharmaceutical therapy for depression and cardiovascular disease is promising, additional studies are needed to gain a complete understanding of this influence. The intent of this review was also to encourage the health care community to implement a multidisciplinary and integrative approach to treating depression and heart disease, which are frequently comorbid and bidirectional, where the alleviation of one condition should prompt the recovery from the other.

Keywords: non-pharmacotherapy, non-pharmacologic therapy, psychotherapy, depression, mental health, mental illness, cardiovascular disease, cognitive behavior therapy, heart disease, major depressive disorder

Table of Contents

What is the Role of Non-Pharmacotherapy in the Treatment of Depression with Cardiovascular Disease?

Chapter 1

Introduction

Depression and cardiovascular disease are two of the most common health conditions in the United States and worldwide (NIMH, 2017; WHO, 2018). Depression, also referred to as clinical depression or major depressive disorder (MDD), is a serious and treatable mental health condition in which individuals experience feelings of sadness and/or a loss of interest in activities that were once enjoyed (American Psychiatric Association, 2013). Major depressive disorder is diagnosed in individuals who experience such feelings of sadness for a period of at least two weeks. While depression refers to a disturbance in the emotional or psychological state, cardiovascular disease refers to a pathophysiological problem with the heart and blood vessels. According to the American Heart Association (2017), cardiovascular disease (CVD), also called coronary artery disease (CAD), refers to diseases affecting the heart and/or circulatory system and consists of various conditions including myocardial infarction, stroke, heart failure, angina, hypertension, arrhythmia, atherosclerotic calcification, and/or heart valve problems (Mezick et al., 2010).

Major depression is known to be more prevalent in people who have experienced a major cardiac event, with up to 40% of patients meeting the DSM-V criteria for major depressive disorder (MDD) (Dhar & Barton, 2016). The large European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) study showed even higher rates of people with cardiovascular disease suffering from comorbid depression, with up to 35% of men

and up to 65% of women measured on the hospital anxiety and depression scale (Dhar & Barton, 2016). Another trial called the enhancing recovery in coronary heart disease (ENRICHD) assessed data on patients who had recently suffered a myocardial infarction and found that depression was diagnosed in a staggering 74% of these patients (Dhar & Barton, 2016). While data shows that an average of 10% of the general population who are hospitalized in general practice clinics suffer from major depression, this percentage increases up to 30% in those with coronary heart disease (CHD) in outpatient clinics, and up to an overwhelming 50% in those who are in inpatient settings recovering from coronary artery bypass surgery (Dhar & Barton, 2016).

The high prevalence of both depression with heart disease begs the question of the possible links between the two health variables. Depression now affects 1 in 15 people or 6.7% of the population in the U.S. and between 3.3% and 21.4% of the global population in both developed and developing countries. Additionally, depression "produces the greatest decrement in health compared with chronic diseases such as angina, arthritis, asthma, and diabetes. The comorbid state of depression incrementally worsens health compared with depression alone, with any of the chronic diseases alone, and with any combination of chronic diseases without depression" (Moussavi et al., 2007). With regard to heart disease, for nearly 15-years cardiovascular disease has persisted as the leading cause of death in the U.S. and worldwide, with ischemic heart disease accounting for 635,260 and 8,756,006 deaths each year, respectively (NIH, 2017; Quirk et al., 2013; WHO, 2018). Recent research on the health effects of depression strongly suggests that mental illness contributes to an increased risk of cardiovascular disease and can be associated with severe cardiovascular consequences (Chaddha, Robinson, Kline-Rogers, Alexandris-Souphis, & Rubenfire, 2016). Certain measures to manage and treat

depression and heart disease utilizing non-pharmaceutical therapies should be considered for their benefits on the psychological and cardiovascular health of patients.

Significance of the Study

A major underlying contributor to the high prevalence of depression and cardiovascular disease around the world may be the evidence of nonadherence to pharmacotherapy most often prescribed in conventional medicine for both disease states. The extent of nonadherence to medication varies widely, and "in different studies it has been recorded as low as 10 percent and as high as 92%. Extensive review of the literature reveals that in developed countries adherence to therapies averages 50%" (Beena & Jimmy, 2011). Studies show that patients are most non-compliant for chronic diseases, such as hypertension (Beena & Jimmy, 2011). Poor adherence to medication regimen has been particularly shown to increase the risk of depression, and patients have a 10-fold increased risk for myocardial infarction and stroke, as compared to patients who follow physician guidance (Chaddha et al., 2016; Lustman & Clouse, 2005). In addition, nonadherence substantially worsens disease, increases risk of death, and increases healthcare costs (Beena & Jimmy, 2011). According to the American Medical Association (2015), there are several reasons for patient nonadherence to physician guidance and prescribed medications including: a fear of potential side-effects, high cost; a misunderstanding for the need of the medication; the patient is already taking too many medications; a lack of symptoms; concerns about becoming dependent on the medication; depression; and a distrust of the physician prescribing the medication. The fear of side-effects and dependence, as well as the high cost of medication are the main deterrents of medication adherence for patients, yet this could be circumvented with the use of more non-pharmaceutical treatment options (American Medical Association, 2015). Through the implementation of various forms of non-pharmaceutical

techniques to treat mental illness and cardiovascular disease, traditional pharmacotherapy and the increased risk of serious adverse events due to noncompliance may be avoided—unless medication is otherwise indicated for the patient where an integrative approach to treatment may be optimal. For this reason, it is important to further investigate the effects of non-pharmacotherapy on depression and cardiovascular disease to better understand the appropriate utilization of non-pharmacological disease management in the scientific and healthcare community. Furthermore, increasing the awareness of depression and cardiovascular disease within the scientific and medical community is imperative for the proper diagnosis, management, and treatment of these health conditions.

This review of literature investigates the effects of various non-pharmacologic therapies on depression and cardiovascular disease and seeks to determine whether common forms of non-pharmacotherapy have positive effects on reducing the symptoms of depression and cardiovascular disease in patients.

Chapter 2

Review of the Literature

Depression and Cardiovascular Disease

Recent interest has been dedicated to investigating the relationship between depression and cardiovascular disease in different populations. In their article, authors Chaddha et al. (2016) discuss the link between mental health and cardiovascular disease. According to Chaddha et al. (2016), the American Heart Association has concluded that depression has the strong potential to accelerate atherosclerosis as well as "promote the onset and severity of the coronary risk factors for diabetes, hypertension, and high levels of low-density lipoprotein." The mechanisms most contributory to an increase in cardiac risk factors through depression is due to lifestyle factors and the lack of compliance with recommended treatments by the patient (Chaddha et al., 2016). Patients with depression or those who experience various symptoms of depression are more likely to engage in unhealthy lifestyle habits including smoking; consuming diets high in calories, salt, and saturated fats; and are less likely to be physically active and adhere to prescribed or suggested medications (Chaddha et al., 2016).

Alcohol use disorder has also been strongly associated with both depression and cardiovascular disease. According to Christy, Anithakumari, and Biju (2017), "a significant number of alcohol use disorder patients also suffer from other psychiatric disorders including mood disorders, anxiety disorders, personality disorders, and schizophrenia," especially depression. The severity of depression corresponds to the severity of the alcohol abuse of patients (Christy et al., 2017). However, heavy drinking (>2.5 drinks/day for women,

>4/drinks/day for men) is associated with an increased risk of cardiovascular disease and death ((O'Keefe, DiNicolantonio, O'Keefe, & Lavie, 2018). Even when men and women drink in moderation, the occasional binge drinking episode offsets the positive effects of moderate drinking (O'Keefe et al., 2018). They also state that "heavy alcohol use is a common cause of reversible hypertension (HTN), nonischemic dilated cardiomyopathy, atrial fibrillation (AF), and stroke (both ischemic and hemorrhagic)." Ethanol itself is a well-documented cardiotoxin if consumed at excess doses. Evidence also suggests that genetic polymorphisms in the aldehyde-dehydrogenase-2 gene plays a significant role in cardiovascular disease as "alcohol oxidase (AOX) is the first enzyme in the methanol utilization pathway and is encoded by two genes, aldehyde-dehydrogenase-1 (ADLH1) and aldehyde-dehydrogenase-2 (ADLH2)" (Cregg, Madden, Barringer, Thill, & Stillman, 1989). Most of the research investigating the effects of an atypical allele for ADLH2 on cardiovascular disease uses the Asian population, since this demographic has a high prevalence of the genetic variation for this gene (Chuan, 2004). According to Luo and Zhang (2004), an atypical ADLH2 gene leads to high alcohol sensitivity and flushing post-drinking. Also, atypical ADLH2 produces a greater risk for alcohol induced liver injury ischemic heart disease (Chuan, 2004). ADLH2 is a multifunctional enzyme that catalyzes the oxidation of aldehydes that is shown to cause mitochondrial cell death and apoptosis (Liu & Sun, 2017). In addition, consuming 14 or more drinks per week has been shown to increase blood pressure in a dose-dependent fashion and any drink above 2 drinks per day increases blood pressure by 1.5 mm/Hg (O'Keefe et al., 2018). With the cessation or drastic reduction of alcohol consumption, alcohol-induced hypertension typically resolves within 2-4 weeks. O'Keefe et al. (2018) state that chronic heavy alcohol consumption is also an independent risk factor for stroke and "a recent meta-analysis of 27 prospective studies reported

that light and moderate alcohol intakes were associated with a lower risk of ischemic stroke, whereas heavy drinking was associated with an increased risk of both ischemic and hemorrhagic strokes." These unhealthy lifestyle factors each independently increase the risk for cardiovascular disease.

Furthermore, patients who do not follow their physician's lifestyle and medication recommendations have a 10-fold increased risk for myocardial infarction and stroke, as compared to patients who follow physician guidance (Chaddha et al., 2016). Chaddha et al. (2016) assert that "there is about an 80% increase in the risk of developing new or worsening cardiovascular disease (i.e., more complications or hospitalizations), as well as death from cardiovascular diseases in adults with depression with or without prior cardiovascular disease. Depression is also common in patients who have angina and can increase the risk of developing myocardial infarction, stroke, sudden death, and atrial fibrillation." For this reason, the importance of patient compliance with physician guidance for the treatment and prevention of both depression and cardiovascular disease should not be underestimated.

While depressed patients have an increased risk of cardiovascular disease due to lifestyle factors and a lack of compliance with treatment recommendations, depression also poses changes in the physiological health of the patient. Depression has been shown to increase circulating cortisol levels within the body—a stress hormone known to increase blood glucose levels, cause weight gain, lower high-density lipoproteins (HDL or "good" cholesterol), as well as increase blood pressure in patients (Chaddha et al. 2016). Patients with depression have also been shown to have higher levels of other circulating hormones, including parathyroid hormone, (Witte et al., 2008). According to an article by Grof, Brown, Grof, and Finkelberg (1980), studies have shown a strong correlation between depression and abnormal neuroendocrine function and "it has been

shown that the neurotransmitter systems that are implicated in the psychobiological mechanisms of affective disorders are involved in the regulation of neuroendocrine function." Additionally, Grof et al. (1980) state that "abnormalities of neuroendocrine function in depressed patients include consistent changes in plasma and urinary cortisol… and in the responsiveness of growth hormone (GH) and thyroid-stimulating hormone." Increased levels of adrenaline in depressed patients have also been linked to an increased resting heart rate, blood pressure, and heart rate response to exertion in patients each may also increase the risk of myocardial infarction, arrhythmias, heart failure, and mortality (Chaddha et al., 2016). According to Chaddha et al. (2016), "inflammation and poor dental hygiene, pneumonia, surgical procedures, and arthritis increase the risk for heart attacks. Depression may also lead to increased platelet activity, increasing the risk of coronary artery occlusion." Poor dental hygiene has been associated with aggravated systemic inflammation through the higher levels of inflammatory circulating molecules including adiponectin, fibrinogen, C-reactive protein (CRP) and cellular adhesion molecule-1 (sICAM-1) (Frisbee, Chambers, Frisbee, Goodwill, & Crout, 2010). A study by O'Neil, Berk, Venugopal, Kim, Williams, and Jacka (2014) asserts that poor dental hygiene is also associated with depression. In their article, O'Neil et al. (2014) state that "poor oral hygiene is associated with a 70% increased risk of CVD, while periodontal disease is associated with a two-fold increase in the risk of CVD-related mortality. There is now abundant evidence that depression is also an inflammatory disorder. This high prevalence condition is accompanied by chronic, low-grade inflammation, indicated by increased levels of acute-phase proteins, such as C-reactive protein (CRP), as well as pro-inflammatory cytokines including interleukins and tumor necrosis factor (TNF)." Furthermore, elevated levels of inflammatory markers including C-Reactive protein, increase the risk of developing major depressive disorder (O'Neil et al.,

2014). Thus, poor dental hygiene is indicated in both cardiovascular disease and major depression.

According to Yeh, Cheng-Li, and Kao (2018), pneumonia is linked to a higher risk of cardiovascular disease particularly heart failure, "regardless of age, gender, comorbidities, and antibiotic use, particularly in elderly male patients [because] streptococcus pneumoniae infects the myocardium and induces necroptosis and apoptosis, which are followed by cardiac scarring and heart failure. Chlamydia pneumoniae and mycoplasma pneumoniae, and the oxidative stress caused by these infections are associated with atherosclerosis in patients with CVDs" (Yeh et al., 2018). Moreover, patients diagnosed with valvular heart disease who undergo non-cardiac surgery have a heightened risk for perioperative cardiovascular risk depending on the severity of the disease (Mutlak, Humpich, Zacharowski, Lehmann, & Meininger, 2011). In the most common form of valvular heart disease, the volume or pressure load of the left ventricle and left atrium typically occurs—thus increasing the patient's risk for heart failure.

Psychosomatic research frequently suggests a strong link between coronary heart disease (CHD) and mental disorders. An article by Chauvet-Gélinier, Trojak, Vergès-Patois, Cottin, and Bonin (2013) discusses how advancements in medical technology including immunohistochemistry, functional imaging, and genetics has made it possible to verify how coronary heart disease and mental illness, mood disorders in particular, are interrelated (Chauvet-Gélinier et al., 2013). Immunohistochemistry has become an indispensable technique used to detect and assess the distribution of proteins in cells of tissues, especially in the carotid body (CB)—a distinct area of the carotid artery that runs along both sides of the throat (Huang, Naduri, Prabhakar, & Walker, 2018). One novel and promising form of functional imaging is the diffuse optical spectroscopic imaging (DOSI)—a non-invasive assessment tool that detects

"silent" cardiovascular disease and cardiovascular disease risk. According to Warren (2017) "DOSI is a quantitative, model-based technique that utilizes a broadband wavelength range, corrects for light scattering, and probes several centimeters into tissue. DOSI is particularly relevant for cardiovascular disease research because it measures absolute concentrations of the primary light absorber in blood, hemoglobin, as well as the oxygenation state of hemoglobin, lipid content, and water content." DOSI makes it possible for hemodynamic measurements, compositional analysis, and reliable comparisons across operators, instruments, and separate institutions (Warren, 2017). With the advancements of medical technologies (MT), increasing attention has been directed towards genetic testing for risk of cardiovascular disease. Next-generation sequencing (NGS-based genetic testing) allows for the "simultaneous testing of all genes associated with any cardiovascular phenotype and molecular genetic testing for multiple genes has become the standard of practice for cardiovascular medicine" (Schmidtke, Wittkowski, & Glaubitz, 2019). There are several advantages to NGS-based genetic testing including increased cost-efficiency, heightened clinical sensitivity, and the increased sensitivity for detecting non-Mendelian phenomena including digenic inheritance (Schmidtke et al., 2019). Genetic testing can also provide insight into the hereditary components of depression. The heritability of major depressive disorder is estimated to be around 40% (Opmeer, Kortekaas, & Aleman, 2010). According to Opmeer et al. (2010), the dopamine theory of affective disorders suggests that a deficiency in dopamine release from presynaptic neurons, impaired signalling, and disturbed catabolism synthesis of dopaminergic transmission could play a significant role in the major symptoms of major depressive disorder. Opmeer et al. (2010) state that:

> "The biosynthesis of dopamine depends on availability of the amino acid tyrosine, which is converted to dihydroxyphenylalanine (dopa) by the enzyme tyrosine hydroxylase.

> Subsequently, the enzyme dopa decarboxylase (DDC) rapidly catalyzes formation of dopamine from dopa. Every biochemical step in the neurotransmission and metabolism of dopamine corresponds to a specific enzyme, encoded for by a corresponding gene. Polymorphisms in these genes could have major implications for dopamine metabolism and neurotransmission and consequently cause neuropsychiatric disorders like MDD."

Therefore, NGS-based genetic testing could be advantageous for the proper diagnosis of both depression and cardiac disorders.

Heart disease and mood disorders are most often comorbid states of illness, with one disease usually worsening the other, and vice-versa. The bidirectional relationship between coronary heart disease and mood disorders has triggered various psychological, biological, and genetic arguments for the relationship between these health conditions (Chauvet-Gélinier et al., 2013). According to Chauvet-Gélinier et al. (2013), "epidemiological studies have shown that depression is a psychic risk factor for coronary heart disease and that coronary heart disease is present in almost 30% of patients with affective disorders." Furthermore, Chauvet-Gélinier et al. (2013) discuss how the natural human stress response to stressful situations may become prolonged leading to the potential for a depressive state in the patient. This depressive state as a result of stress may then lead to physiopathological alterations of the heart.

It is equally important to recognize the adverse effects of blood sugar imbalance with mood regulation and the increased incidence of depression "particularly operational in type 1 diabetes, wherein the onset of diabetes antedates the first presentation of depression by many years" (Lustman & Clouse, 2005). Research shows that hyperglycemia can promote and exacerbate symptoms of anxiety in patients suffering from type I diabetes (Lustman & Clouse, 2005). Moreover, Lustman and Clouse (2005) state that in "a study that prospectively examined

the relationship between blood glucose levels and self-reported mood in adults with type 1 diabetes, negative mood states, including anger and sadness, were related to high blood glucose levels in the majority of patients." Thus, the effects of glucose dysregulation, particularly hyperglycemia, including cortisol abnormalities, weight gain, physical inactivity, and the poor adherence to medication regimen—have all been shown to increase the risk of depression in patients, though the directional relationship has not yet been fully established (Lustman & Clouse, 2005).

Research also suggests an association between hypoglycemia, depression, and sleep quality in patients with type II diabetes. A meta-analysis by Biggers et al. (2019) discusses how poor sleep quality, excessive daytime sleepiness, and depressive symptoms are related to hypoglycemia, which is recognize as a relationship "that may be complex, bidirectional, and reflect poor self-care, non-adherence to diet or glucose self-monitoring." Hypoglycemia is defined as experiencing episodes of low blood sugar and usually mild symptoms including sweating, trembling, or difficulty concentrating (Biggers et al., 2019). Results of their study indicated that adults with type II diabetes in Chicago and Thailand who had a history of hypoglycemia were more likely to experience poor sleep quality and higher depressive symptoms in bivariate analysis. Furthermore, subjects from Thailand had "more depressive symptoms were associated with more frequent hypoglycemia, adjusting for insulin and sulfonylurea use as well as duration of diabetes" (Biggers et al., 2019) Thus, a correlation between poor glucose control and depression has been shown to exist for in both hyperglycemia and hypoglycemia.

According to Lustman and Clouse (2005), psychotherapy and pharmacotherapy are both effective for the treatment of diabetes; "both cognitive behavior therapy and selective serotonin

reuptake inhibitors are weight neutral and have been associated with glycemic improvement in some studies." The exact nature explaining the comorbidity of depression and coronary heart disease has not yet been clearly established. However, the INTERHEART study reported that depression as a psychic factor and psychosocial stressor is the third leading risk factor for coronary artery disease behind apolipoprotein ratio B/apolipoprotein A1 and smoking. Depression also has a higher risk ratio for coronary heart disease compared to diabetes, arterial hypertension and abdominal obesity and evidence indicates that treating a comorbid affective disorder can decrease substance abuse and craving in patients (Chauvet-Gélinier et al. 2013; Quello, Brady, & Sonne, 2005).

Interestingly, personality type has been shown to increase one's risk of developing coronary artery disease due to adverse long-term biological mechanisms within the body. Chauvet-Gélinier et al. (2013) describe how people with type A personality characterized by intense activity, a desire to do things quickly and combativeness "that may lead to hostile attitudes in order to reach fixed objectives. The behavior pattern of type A people confers great vulnerability to depression." Furthermore, people with type A personality are more likely to develop depression and coronary heart disease as a result of mood disorders as a response to unwanted life circumstances including being unrecognized at work, unemployment, or social isolation (Chauvet-Gélinier et al., 2013). Also, patients who have suffered from myocardial infarction are more likely to have type A personalities (Chauvet-Gélinier et al., 2013). Likewise, these people are also more inclined to suffer from mood disorders, usually major depressive disorder (Chauvet-Gélinier et al., 2013). Another article by Rugulies (2002) discusses how the plethora of research assessing the association between depression and cardiac health blames the effects of depression on cardiovascular disease on behavior patterns—

particularly the type A personality type and the tendency for these people to "wear themselves down." Rugulies (2002) describes the type A personality as individuals who display hard-driving behavior, including competitiveness and chronic feelings of time-urgency—which is acknowledged by the scientific community as an independent risk factor for coronary heart disease. In recent years, the continued investigation on psychic disorders and cardiovascular disease has shed light onto the revelation that "depression is a predictor for survival after myocardial infarction" (Rugulies, 2002).

Lifestyle factors have also been shown to increase the risk of cardiovascular disease. Chauvet-Gélinier et al. (2013) describe the behavioral impact of depression on the negative evolution of heart disease. People who are depressed are characterized by a loss of interest in activities, a lack of motivation to do things they once enjoyed, and generalized feelings of malaise and sadness. Those who are depressed are less likely to feel motivated to change unhealthy daily habits, such as smoking, consuming high-calorie foods, and are unable to muster the energy to maintain physical fitness. Unfortunately, depression "may occur at any time during a person's history of coronary artery disease and is a behavioral factor in the development or aggravation of heart disease as the patient adopts a prolonged sedentary lifestyle, experiences a decline in psychological and physical motivation and tends not to respect the therapeutic regimen" (Chauvet-Gélinier et al., 2013). Additionally, symptoms of depression increase the risk of developing metabolic syndrome especially among middle-aged women (Chauvet-Gélinier et al., 2013). Metabolic syndrome is a cluster of conditions including hypertension, dyslipidemia, elevated fasting blood glucose, and abdominal obesity (Levine et al., 2017). Moreover, changes in metabolism as a result of depression increase the risk of coronary artery disease in this population.

A study by Ornish et al. (1990) investigated whether comprehensive lifestyle changes affect coronary atherosclerosis. A group of 48 patients with angiographically documented coronary artery disease between the ages of 35 and 75 years were assigned to one-of-two groups. A total of 28 subjects were assigned to an experimental group where subjects were required to follow low-fat vegetarian diets, smoking cessation, stress management training, and moderate exercise for at least one year. The second group of 20 patients were assigned to a usual-care control group. Selective coronary angiography was done using the percutaneous femoral technique. Blood samples to measure serum lipids were drawn at baseline, after 6 months, and after one year. Nutrient intake and dietary adherence were assessed using a 3-day diet diary at baseline and after one year. Stress management techniques were given for at least one-hour per-day with an audiocassette tape to assist in stretching exercises, breathing techniques, meditation, progressive relaxation, and imagery (Ornish et al., 1990). Patients were asked to participate in daily physical exercise and advised to reach a target training heart rate of 50-80% of their heart rate at baseline. Subjects were asked to engage in 3 hours of physical exercise (walking) each week in 30-minute increments. Patients in the experimental group also participated in twice-weekly group discussions in which a clinical psychologist provided social support to patients to help them adhere to these lifestyle changes, enhance communication skills, and to talk about their feelings about relationships, work, and home life (Ornish et al., 1990).

After the evaluation of the various measures for serum lipids, coronary atherosclerosis through angiography, diet diary, and physical exercise performance, results of Ornish et al.'s (1990) study concluded that lifestyle changes have a significant positive effect on cardiovascular health. A total of 84% of patients in the experimental group who engaged in lifestyle changes had a regression of coronary atherosclerosis, where the average percentage diameter stenosis

regressed from 61.1 mm to 55.8 mm. However, the usual-care group experienced a worsening of coronary atherosclerosis since percentage diameter of stenosis increased by an average of 61.7 mm to 64.4 mm at the end of one year (Ornish et al., 1990). Furthermore, the degree of adherence to lifestyle changes was directly related to the degree of improvement of coronary atherosclerosis in patients.

While the lifestyle and biological factors as side effects of depression are shown to increase the incidence of cardiovascular disease in patients, heart rate variability (HRV) is another indicator of heart disease. Heart rate variability "indicates the homeostasis between the sympathetic and parasympathetic systems in the regulation of the heart rate and involves several cholinergic and monoaminergic neurotransmitters" including acetylcholine, serotonin (5-HT), and dopamine—all key neurotransmitters in mood disorders and important indicators for the progression of myocardial infarction (Sparks et al., 1992; Chauvet-Gélinier et al., 2013). Moreover, depression also adversely affects heart rate variability in patients. Research has shown that subjects with depression are at an increased risk of sudden postinfarction death due to lowered heart rate variability (Chauvet-Gélinier et al., 2013). Thus, "decreased heart rate variability exposes patients with simultaneous coronary artery disease and major depression to ventricular arrhythmia and excess mortality" (Chauvet-Gélinier et al., 2013).

Cardiovascular Disease, Depression, and Inflammation

According to Chauvet-Gélinier et al. (2013), the comorbid state of depression and cardiovascular disease increases inflammation and oxidative stress in patients. Research has shown strong evidence suggesting that "increased concentrations of blood markers of inflammation (interleukin-1, interleukin-6, tumor necrosis factor-alpha) have been found in both depression and heart disease" (Chauvet-Gélinier et al., 2013). Additionally, a simultaneous

decrease in serum concentrations of omega-3 polyunsaturated fatty acids that hold anti-inflammatory properties has also been noticed in patients experiencing both depression and cardiovascular disease (Chauvet-Gélinier et al., 2013). Moreover, psychosomatic research has frequently noted the strong association between inflammatory markers, oxidative stress, and mood disorders in subjects. Most psychiatric disorders increase membrane lipid peroxidation mediated by reactive oxygen species (ROS) in patients (Chauvet-Gélinier et al., 2013). These reactive oxygen species are damaging to the body and "may be ischaemic, inflammatory, or caused by psychological stress due to depression" (Chauvet-Gélinier et al., 2013.

Another frequent association in the comorbid state of cardiovascular disease and mood disorders is a hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis. Depression is considered a major stressor to the body and thus, the HPA axis in patients with depression becomes strongly activated (Chauvet-Gélinier et al, 2013). As a result of HPA activation, elevated levels of serum cortisol urinary derivatives can be seen in depressed patients, which is the body's attempt to sustain the disrupted homeostasis. Hypercortisolemia "could induce glucose and lipid metabolism, leading to increased amounts of visceral fat and insulin resistance, both of which contribute to the development of metabolic syndrome through the activation of proinflammatory mediators" (Chauvet-Gélinier et al., 2013). Chauvet-Gélinier et al. (2013), suggest that a disruption in the HPA axis as a result of depression could increase atherosclerosis in patients, thereby increasing the risk of the comorbidity of coronary heart disease.

Various forms of arthritis also have shown to increase the risk of developing cardiovascular disease due to the increased circulating inflammatory compounds. In particular, patients with "rheumatoid arthritis (RA) suffer cardiovascular events 1.5 - 2 fold greater than the general population, and cardiovascular (CV) events are the leading cause of death in patients

with RA," A more recent study showed that women with rheumatoid arthritis have a two-to-three fold increase in myocardial infarction with or without prior coronary risk factors (Blum & Adawi, 2019). Blum and Adawi (2019) strongly suggest that increased systemic inflammation is the main culprit in the heightened risk for cardiovascular disease in patients with RA. This is also considered responsible for the increased risk of cardiovascular disease in patients with poor dental hygiene, pneumonia, surgery, and those suffering from depression. Additionally, patients with RA have been shown to have a greater risk of developing both anxiety and depression (Li, Chou, Chen, Lu, & Chang 2019). According to Li et al. (2019), after examining 113 patients with RA compared to 42 healthy controls, those with RA had significantly higher levels of "serum proinflammatory cytokine levels, including interleukin (IL)-1[beta], IL-6, IL-17 and tumor necrosis factor-alpha (TNF-[alpha])…as were the mean anxiety and depression subscale scores." From this research, Chaddha et al. (2016) urge health professions and the public to acknowledge mental illness as a priority in the medical community. They encourage further research on the association between depression and cardiac health, as well as to discover new measures for the prevention and treatment of mental and cardiovascular disease.

Chauvet-Gélinier et al. (2013) also describe a genetic association between psychic disorders and cardiovascular disease. Recent research investigating the similarity between depression and cardiovascular disease has found that patients with both health conditions have shorter telomeres, which are "genetic markers of oxidative stress that trigger cell death when the length reaches a critical threshold" (Chauvet-Gélinier et al., 2013). It has been shown that the length of telomeres, when measured in circulating leukocytes, becomes reduced in both depression and coronary artery disease "illustrating in both cases the impact of oxidative stress at the initial level of genetic machinery" (Chauvet-Gélinier et al., 2013). Additionally, recent

research highlights a disturbance in the synthesis of cardiac protective anti-inflammatory omega-3 fatty acids due to an impairment in this metabolic pathway in depressed and cardiac patients (Chauvet-Gélinier et al., 2013). Research also presents the health benefits of omega-3 fatty acids especially in their ability to reduce the "risk of primary cardiac arrest/sudden cardiac death, presumably owing to their antiarrhythmic properties. A notable depletion of red blood cell membrane omega-3 fatty acids has been reported in major depression." Also, "a decreased omega-3 fraction in cholesterol esters and an increased arachidonic acid (omega-6)–eicosapentaenoic acid (omega-3) ratio in cholesterol esters and phospholipids of major depressed subjects compared with minor depressed subjects and healthy controls has been found" (Severus, Ahrens & Stoll, 1999). Furthermore, the mechanisms by which omega-3 fatty acids lower cardiac risk factors include a reduced ventricular arrhythmia, thrombosis, triglycerides, atherosclerotic plaque, inflammation and hypertension, and endothelial relaxation (Parletta et al., 2016). According to Parletta et al. (2016), cardiovascular disease is 30% higher in people with mental illness comparing to the general population. Likewise, "erythrocyte docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) (omega-3 index) 4% is a marker for increased mortality risk from CVD while 48% is protective. Meanwhile, "omega-3 polyunsaturated fatty acids are also important for brain function and may ameliorate symptoms of mental illness" (Parletta et al., 2016). Inflammation has been proposed as a possible mediating role for comorbid physical and mental illness and may be one of the mechanisms by which omega-3 polyunsaturated fatty acids exert their effects. Additionally, the anti-inflammatory properties of eicosanoids that are produced by eicosapentaenoic acid are capable of counteracting the inflammatory properties of eicosanoids which are produced by arachidonic acid from the omega-6 polyunsaturated fatty acids. Researchers Parletta et al. (2016) recognize this as a concern in

"Western societies that have increased the intake of n-6 PUFA via vegetable oils and processed foods while decreasing intake[s] of n-3 PUFA from nuts, seeds, dark leafy vegetables, and fatty fish." A more severe depressive state has also been associated with a decreased red blood cell content of omega-3 fatty acids as well as a reduced intake of polyunsaturated lipids as compared to those with less severe depressive symptoms (Severus et al., 1999). In further support of these findings, a group of Canadian researchers investigated the levels of omega-3 polyunsaturated fatty acids in subjects who had undergone an acute myocardial infarction and who were also suffering from major depression. These subjects were found to have significantly lower levels of omega-3 polyunsaturated fatty acids and omega-3 indexes at 4.46% compared to those without depression at 5.05% (Parletta et al., 2016).

The association between depression, cardiovascular disease, and omega-3 fatty acids centers on research strongly suggesting that depressed patients have lower heart rate variability (a risk factor for sudden cardiac death) than the general population (Severus et al., 1999). Supplementation with fish oils has shown to increase heart rate variability in these patients, thereby reducing their risk for depression and sudden cardiac death (Severus et al., 1999). Further research investigating the genetic influences of lipid metabolism, depression, and cardiac health is encouraged. Meanwhile, a study by McCaffery et al. (2009) found a genetic vulnerability in 977 subjects with cardiopathy. This subject population was found to have a "single nucleotide polymorphism in the gene coding for Willebrand factor in the onset of depression secondary to heart disease" (Chauvet-Gélinier et al., 2013). Thus, the pathophysiological and genetic link between depression and cardiopathy should be further investigated.

Evidence also suggests a sympathetic hyperactivity and disturbance in platelet reactivity in comorbid depression and cardiovascular disease. According to Chauvet-Gélinier et al. (2013), studies have shown increased levels of noradrenaline in patients with depression, as well as increased heart rates in these patients. Moreover, "this excessive stimulation of the sympathetic system develops and aggravates coronary artery disease via a double deleterious effect on heart function itself and on platelet aggregation, which is diminished" (Chauvet-Gélinier et al., 2013). Additionally, platelet hyperactivation in depression may lead to an increased risk of cardiovascular disease. Platelets contain serotonin receptors that play a role "in both hemostasis and coronary vasoconstriction via this monoamine," which could exacerbate coronary disease by promoting ischaemic mechanisms (Chauvet-Gélinier et al., 2013). One theory on the relationship between depression and cardiovascular disease proposes a common underlying pathophysiological process, particularly involving psychosocial stress in which serotonin is involved (Steiner, 2011). Stress creates a pro-inflammatory cytokine response with the inflammatory molecules Interleukin-1, tumor necrosis factor-alpha, and Interferon-c (Steiner, 2011). According to Steiner (2011), "these cytokines act as mediators of the behavioral neuroendocrine (HPA axis hyperactivity) and neurochemical (reduction in 5-HT levels by lowering the availability of its precursor tryptophan) features of depression. These same pro-inflammatory cytokines disrupt 5-HT levels not only in the central nervous system but also in the periphery, causing platelet aggregation, which leads to arteriosclerosis." While a reduction of serotonin results in platelet aggravation and thus an increased risk for CVD, the simultaneous effects for an increased risk of depression are also evident.

It is well-documented that the neurotransmitter serotonin plays a vital role in the behaviors disrupted in depression, including mood, sleep and appetite. It is suggested that an

imbalance between the ratio of 5-HT1A and 5-HT2A receptors may underlie depressive disorders (Steiner, 2011). Further, serotonin, one of the main neurotransmitters contributing to mood, converts to melatonin from tryptophan. Peuhkuri, Sihvola, and Korpela (2012) discuss the neurohormone melatonin, which is "secreted predominantly at night and is important in conveying the daily cycle of light and darkness to the body, thus regulating circadian rhythms and helping us to fall and stay asleep." It is known that the pineal gland in the brain contains high levels of both omega-6 and omega-3 polyunsaturated fatty acids, especially arachidonic acid and docosahexaenoic acid (DHA). According to Peuhkuri et al. (2016), evidence shows that the synthesis of fatty acids has an effect on melatonin production. In one study, rodents who were fed a diet deficient in omega-3 fatty acids had a reduced synthetization of night-time melatonin. However, with DHA supplementation, levels of melatonin returned to normal. This association again reiterates the relationship between omega-3 fatty acids, mental, and cardiac health. One key element of melatonin production is that it is synthesized from tryptophan (tryptophan > serotonin > melatonin), an essential dietary amino acid. Thus, research has shown that nutritional factors, including the dietary intake of vegetables, caffeine, vitamins, and minerals, has the potential to modify melatonin production. Dietary influences on melatonin production still have less of an impact than light, which is the "most dominant synchronizer of melatonin production" (Peuhkuri et al., 2016). Hence, serotonin has shown to be one key factor in the progression of comorbid depression and cardiovascular disease and additional research should be conducted to confirm these findings.

Research further suggests an association between the circadian rhythm, depression, and heart disease. According to Chauvet-Gélinier et al. (2013), the scientific research community has recently shown interest in rhythms in mood disorders, particularly the sleep cycle and

depression. Evidence shows that people who have depression usually experience greater sadness during the morning hours and feel better as the evening arises. The common expression of "the morning blues" reflects this intriguing phenomenon. Chauvet-Gélinier et al. (2013) state that "alterations in the secretions of biochemical mediators (cortisol, thyroid-stimulating, melatonin, etc.)" can be applied to the circadian rhythm and depression. Moreover, a similar rhythmic phenomenon can be seen with both depression and heart disease. Studies have shown that humans have a genetic internal clock that also applies to a circadian aortic expression of the heart. According to Chauvet-Gélinier et al. (2013), while it is probably impossible to "establish absolute links between cardiovascular disease and depression via a dysfunctioning circadian system, it is well known that circadian desynchronization leads to both affective disorders and cardiac complications." Chauvet-Gélinier et al. (2013) note that further investigation linking depression, cardiovascular disease, and a genetic connection to the circadian system should be encouraged.

Researchers Mezick, Hall, and Matthews (2010) also discuss the key associations between sleep, depression, and cardiovascular disease. In their literature, Mezick et al., (2010) state that approximately 50% to 90% of depressed patients complain of sleep disturbance as sleep and depression are highly related conditions. Mezick et al. (2010) located eight longitudinal studies examining the relationship between sleep and depression, and cardiovascular disease as the outcome measurement. The large-scale studies were comprised of middle-aged and older-aged community-dwelling adults. The study duration was between 3 and 12 years. Subjects were given questionnaires to assess depressed mood, except for one study that asked only one question about depressed mood. Exclusion criteria included subjects with baseline cardiovascular disease, with the exception of one study that accounted for baseline disease and

cardiovascular health (Mezick et al., 2010). Results of their meta-analysis concluded that "six of the eight studies reported significant associations among components of poor sleep continuity and CVD, after adjusting for depression, whereas two did not." Four of the studies assessed found that depression or some other form of psychological distress predicted cardiovascular disease in patients, regardless of sleep continuity. Moreover, Mezick et al. (2010) concluded that "most of the extant literature suggests that both poor sleep continuity and depression are independent risk factors for CVD, although there is some variation in individual study results." Thus, sleep and any disruption in the circadian rhythm have shown an association with depression and CVD.

Genes have also been shown to play a role in the circadian rhythm, depression, and cardiovascular disease. According to Mezick et al. (2010), some evidence proposes that the covariation among sleep parameters, depressive symptoms, cardiovascular disease, and diabetes may be partially due to genetic influences. A study examining twins showed that common genetics significantly influenced the phenotypic correlations between depressive symptoms and problems with sleep in children. Common genes in twins were also shown to play a major role in the physical manifestation of depressive symptoms and coronary artery disease (Mezick et al., 2010). Despite these findings, there is a small number of studies investigating the effects of sleep on comorbid depression and cardiovascular disease through the mechanism of a shared genetic vulnerability. An interesting theory on genes implicated in sleep regulation has also been postulated. According to Mezick et al. (2010), "disruptions of the core CLOCK genes that regulate endogenous circadian rhythmicity are linked to perturbations in glucose metabolism, adipocyte function, and vascular function, and others have theorized that clock genes may be implicated in the development of mood disorders." Circadian CLOCK genes are "any of a

number of genes that interact with each other to make up an auto-regulatory feedback loop, in which its activation and repression cycle takes about one day. CLOCK genes are components of the circadian clock comparable to the cogwheels of a mechanical watch. They interact with each other in an intricate manner generating oscillations of gene expression." (Albrecht & Ripperger, 2008). It is also believed that genetic variation may be responsible for biobehavioral pathways that increase the susceptibility to inflammation, HPA axis disruption, and an imbalance of the autonomic system—all contributing to the interrelatedness of sleep disruption, depression, as well as cardiometabolic disease in the patient (Mezick et al., 2010). However, in order to further establish this link, research is needed examining whether depression or cardiovascular disease, or their comorbid state, increases the propensity for sleep disturbance, and vice-versa.

Finally, Chauvet-Gélinier et al. (2013) provide readers with clear and thorough explanations of the various research associations between affective disorders, particularly depression and coronary heart disease. From their discussion, the bidirectional relationship between depression and cardiovascular disease is described via fundamental multidimensional processes including behavior and psychological features, heart rate variability, inflammation, oxidative stress and activation of the HPA axis, the impact of stress, sympathetic hyperactivity and disturbances in platelet activity, and genetic markers of vulnerability to both depression and cardiovascular disease, as well as how the circadian system is related. Additional research is needed to better understand the association between genetic variations and the circadian system in relation to depression and coronary artery disease.

One of the earlier studies investigating the association between depression and heart disease by Ford et al. (1998) aimed to determine if clinical depression is an independent risk factor for incident coronary artery disease. Ford et al. (1998) used data from the John Hopkins

Precursors Study to determine such a link. The John Hopkins Precursor Study was a prospective observational study of 1190 male medical students enrolled in between 1948 and 1964. These subjects continued follow-up throughout medical school and during the mean 37–year follow-up period. Researchers collected information on family history, health behaviors, and clinical depression (Ford et al., 1998). Ford et al. (1998) emphasized that "depression requires that a number of symptoms be present simultaneously for several weeks" and argue that, unlike other studies, the John Hopkins Precursor Study "has collected data on episodes of clinical depression, coronary artery disease risk factors, and coronary artery disease for more than 35 years and provides a unique opportunity to determine if individuals who have has an episode of clinical depression are at increased risk for the development of coronary artery disease." Results of the John Hopkins Precursor study indicated that one hundred thirty-two men reported symptoms of depression during the study follow-up period. The average age of the first episode of depressive symptoms was 40 years, while a greater number of subjects who reported depression during follow-up were older (27 vs. 26, P=.03) at completion of medical school. Additionally, of the depressed subjects, 23% reported not seeking medical treatment for clinical depression, 33% reported the use of antidepressant medications, and 44% of depressed subjects reported seeking psychotherapy with or without the use of benzodiazepines or other sedative drugs (Ford et al., 1998). The risk factors for cardiovascular disease were reported through "exercise, serum cholesterol levels, smoking, blood pressure, diabetes, and history of parental myocardial infarction" and were assessed during medical school using questionnaires, examinations, and blood tests (Ford et al., 1998). Annual questionnaires, National Death Index searches, medical records, death certificates, and autopsy reports were used to assess the status of subjects. At the conclusion of the study, investigators used collected data to determine that "clinical depression

was associated with an almost 2-fold increased risk for subsequent coronary heart disease" (Ford et al., 1998). After adjusting for body mass index, family history of premature parental myocardial infarction, baseline serum cholesterol level, and time-dependent report of hyperlipidemia required treatment, the increased risk of coronary artery disease in these depressed subjects remained statistically significant (relative risk (RR), 1.7; 95% confidence interval [CI], 1.0-2.9) (Ford et al., 1998).

Limitations of the John Hopkins Precursor Study include aspects of the study population. Approximately 98% of the subjects were white males; an obvious lack of racial diversity interferes with the accuracy of applying these study results to the general population comprised of diverse ethnicities. Furthermore, the study population only included male subjects. Thus, results of the study cannot be applied to the female population. Another important limitation to consider is the highly educated study populous. Medical school students are more informed on the adverse health circumstances of negative lifestyle habits, including unhealthy diets, smoking, and a lack of physical exercise than the general population. Moreover, informed subjects are more aware of the symptoms and potential causes of depression and cardiovascular disease, thereby more likely to engage in activities and strategies for disease prevention. Future research should control for intervening variables that may affect the relationship between the variables being studied through increased randomization, restriction, and matching prior to the execution of the study. Additionally, if potential intervening variables exist following data collection, regression models can be used to adjust for them so that the true nature of the correlations between variables can be presented.

In order to quantify the impact of depression on the development of coronary heart disease in initially healthy subjects, Rugulies (2002) conducted a systematic review of several

cohort studies discussing this association. Rugulies (2002) used the search engines MEDLINE, PSYCHINFO, bibliographies, expert consultations, and personal reference files for studies on depression and cardiovascular disease in healthy populations. A total of eleven studies met the inclusion and exclusion criteria set forth by Rugulies (2002) which consisted of prospective cohort studies on initially healthy subjects with depression as the predictor and coronary heart disease as the outcome measurement. Types of exposure included unipolar clinical depression and depressive mood—both terms refer to "depression." Eligible outcomes of depression and coronary artery disease included fatal and nonfatal myocardial infarction, coronary death, and cardiac death. Certain exclusion criteria were also listed: case-control and cross-sectional studies, bipolar disorders and the outcome of angina pectoris (Rugulies, 2002). Results of Rugulies' (2002) review indicated that in 7 of the 11 studies, "depression was associated with a significant increased risk of coronary heart disease," including all 3 of the studies that measured for clinical depression with relative risks (RRs) ranging from 1.50 (95% CI=1.02-2.19) to 4.16 (1.49-11.62) (Rugulies, 2002). Moreover, the other 4 studies showed a positive association between depression and cardiovascular disease, however, findings were inconsistent.

The limitations of Rugulies' (2002) meta-analytic review included publication bias; all studies in the review were published, therefore research linking clinical depression to cardiovascular disease that may have been unpublished were not accounted for. Additionally, Rugulies (2002) acknowledges his use of very strict inclusion and exclusion criteria for his review. This is especially true of his exclusion of research pertaining to angina pectoris for eligible outcomes since angina pectoris is a significant manifestation of coronary heart disease. Rugulies (2002) was also unable to investigate the dose-response relationship between depression and cardiovascular disease in his review and clinical depression being a strong

predictor of heart disease points to a likely dose-response relationship. Finally, none of the studies assessed the effects of mild symptoms of depression on cardiovascular disease—a topic for further research.

Various cardiovascular health metrics have been assessed for their correlation to depression among adults in the United States. According to Zhang, Jackson, Merritt, Gillespie and Yang (2019), while death rates over the past several decades have declined, death from cardiovascular disease remains the leading cause of death in the United States and resulted in 30.8% (or 800,937) of all deaths in 2013 (Zhang et al.,2019). Zhang et al. (2019) state the following:

> "The total direct medical costs of [cardiovascular disease] are projected to increase to $918 billion by 2030. A substantial body of evidence demonstrated that individuals with favorable levels of major [cardiovascular] risk factors experienced a significant reduced risk of cardiovascular incidence and mortality."

The American Heart Association recognizes seven cardiovascular health metrics, consisting of four health behaviors and three health factors. The four health behaviors include body mass index, smoking, physical activity, and dietary intake. The three health factors include total cholesterol, blood pressure, and fasting glucose (Zhang et al., 2019). The American Heart Association asserts that all seven cardiovascular health factors are modifiable and can be categorized into three levels: poor, intermediate, and ideal health.

Moreover, Zhang et al. (2019) recognize depression as one of the most common chronic conditions in general practice, affecting 1 in 10 patients and over 311 million people worldwide (Zhang et al., 2019). Zhang et al. (2019) state that depression is an independent risk factor for "increased morbidity and mortality, lower functional status, and [worsens] quality of life as well

as [increases] costs." In a survey of 245,404 adults from over 60 countries, comorbid depression was found to be worse for health outcomes of patients than those suffering from asthma, diabetes, arthritis, or cardiovascular disease alone (Zhang et al., 2019). Thus, in their article Zhang et al. (2019) investigated the relationship between different health metrics of cardiovascular as set forth by the American Heart Association, and clinical depression using nationally representative samples.

Researchers Zhang et al. (2019) used data from the National Health and Nutrition Examination Survey (NHANES) that ran from 2007-2014 to find correlations between depression and cardiovascular disease. The NHANES study "uses a complex, stratified, multistage probability cluster sampling, cross-sectioning design to collect health and nutritional data from a representative sample of the noninstitutionalized U.S. population" (Zhang et al., 2019). A total of 14,561 participants aged 20 years or older met the inclusion and exclusion criteria set forth by Zhang et al. (2019). All participants completed a reliable 24-hour dietary recall. Pregnant women, subjects with missing cardiovascular health metrics scores, depression scores, BMI scores, and those with BMIs of less than 18.5 kg/m^2 were excluded from the study. Subjects with a history of cardiovascular disease (myocardial infarction, congestive heart failure, and stroke) and participants with cancer were also excluded from the study (Zhang et al., 2019). Zhang et al. (2019) used the Healthy Eating Index 2010 (HEI-2010) scores to assess dietary patterns of subjects. The HEI-2010 is based on a 12-component index for total fruit, whole fruit, total vegetables, grains and beans, whole grains, dairy, total protein foods, seafood and plant protein, fatty acid, refined grains, sodium, and empty calories. Possible scores ranged from 0 to 100—higher scores indicating a healthier diet (Zhang et al., 2019).

Symptoms of depression were gathered using the Patient Health Questionnaire (PHQ-9), "a validated nine-item screening instrument that asks about the frequency of depressive symptoms over the past 2 weeks" with "not at all," "several days," "more than half the day," and "nearly every day" as possible responses (Zhang et al., 2019). Additionally, the NHANES was analyzed for depressive symptoms with adjustments for age, gender, race and ethnicity, education, and alcohol use. Results of Zhang et al.'s (2019) study concluded that there is a strong and graded association between mild, moderate, and severe depressive symptoms and cardiovascular health metrics among U.S. adults. From this research, Zhang et al. (2019) also found that participants with fewer cardiovascular health metrics had an increased risk for experiencing symptoms of depression and these results were consistent among various subgroups.

Furthermore, Li et al. (2015) investigated the relationship between cardiovascular health (CVH) and depression among 6,851 men, 20 years or older, living in the Tangshan City of China. Researchers used seven CVH metrics including smoking, body mass index, dietary intake, physical activity, blood pressure, total cholesterol and fasting blood glucose to assess ideal heart health. Participants were measured for depression using the Epidemiologic Studies Depression Scale (CES-D) and any score of 16 or above was indicative of depressive status (Li et al., 2015). Li et al., (2015) analyzed the relationship between cardiovascular health metrics and depression using logistic regression. Of the 6851 subjects in the study, 7.7% were found to suffer from depression. After adjusting data for the potential of confounding variables, Li et al. (2015) found that "men in the highest quartile of ideal CVH metric summary score had a reduced likelihood of having depression compared to those in the lowest quartile." Thus, Li et al. (2015)

suggest that improved CVH status is associated with a lower risk of depression in Chinese men over the age of 20.

A study by Espana-Romero et al., (2013) also investigated the relationship between ideal cardiovascular health and the likelihood of depressive symptoms. A total of 5110 participants were gathered from the Aerobics Center Longitudinal Study, which progressed between 1987 and 1998. Researchers included subjects who did not present with any mental disorder/condition at baseline. Espana-Romero et al. (2013) considered various ideal cardiovascular health behaviors which included never smoking, body mass index <25g/m2, physical activity, and appropriate diet consistent with guideline recommendations. Blood pressure (<120/80mm Hg), total cholesterol (<200mg/dL) and fasting blood glucose (<100mg/dL) were measured at baseline for all participants. At the conclusion of the study, Espana-Romero et al. (2013) found that of the 5110 participants, 641 reported depressive symptoms indicated using the 10-item Center for Epidemiologic Studies Depression Scale in 1990, 1995, or 1999. Results of the study suggest that ideal cardiovascular factors pose an inverse relationship with symptoms of depression (Espana-Romero et al., 2013).

According to Moussavi, Chatterji, Verdes, Tandon, Patel, and Ustun (2007), depression is one of the leading causes of *disease* worldwide. Additionally, "depression produces the greatest decrement in health compared with the chronic diseases' angina, arthritis, asthma, and diabetes. The comorbid state of depression incrementally worsens health compared with depression alone, with any of the chronic diseases alone, and with any combination of chronic diseases without depression (Moussavi et al., 2007). Therefore, Moussavi et al. (2007) urge the public to address depression as a worldwide health crisis and a public-health priority.

Researchers Hare et al. (2014) also confirm findings that patients with cardiovascular disease have higher rates of depression than the general population. Also, Hare et al. (2014) propose that people who suffer from depression are more likely to develop cardiovascular disease and have an increased risk of all-cause mortality as compared to the rest of the population. The relationship between depression and cardiovascular disease is graded—the more depressed an individual, the more severe the cardiovascular disease. The detection of depression in cardiovascular disease patients is important. According to Hare et al. (2019), "depression is arguably the single most important driver of quality of life and therefore needs to be prevented and appropriately managed if it is subsequently detected in CVD patients." It goes without refute that the lower the quality-of-life of an individual, the increased risk for depression, and thus the increased risk for cardiovascular disease—especially since the relationship between depression and cardiovascular disease has become well-established.

Chapter 3

Methods

A comprehensive review of the literature on depression, cardiovascular disease, non-pharmacotherapy, and psychotherapy was conducted.

Procedures

Search procedure. A careful review of the literature related to non-pharmacotherapy, depression, and cardiovascular disease was conducted. The review highlighted the following topics: (a) psychotherapy, (b) depression, (c) cardiovascular disease, (d) major depressive disorder, (e) non-pharmacotherapy, (f) cognitive behavior therapy, (g) meditation, (h) acupuncture, (i) physical exercise, and (j) mindfulness therapy.

Libraries used. There was one library used for the search for sources for this project. The Wahlstrom Library at the University of Bridgeport was used for this review.

Search engines and databases used. The following databases were used to search for the sources for this review: PubMed, EBSCOhost, Google, and Google Scholar.

Search terms. Several search terms were used to identify sources for this review. The search terms included (a) non-pharmacotherapy, (b) depression, (c) cardiovascular disease, (d) major depressive disorder, (e) cognitive behavior therapy, (f) psychotherapy, (g) meditation, (h) acupuncture, (i) physical exercise, and (j) mindfulness therapy.

Age of the sources and significant literature was reviewed. Sources from the year 1980 and above have been considered for inclusion in the review of the literature.

Inclusion criteria. There were four inclusion criteria. Inclusion criteria included (a) literature published since 1980; (b) English-language text; (c) peer-reviewed articles; and (d) Websites relating to non-pharmacotherapy, psychotherapy, depression, and cardiovascular disease.

Exclusion criteria. There were four exclusion criteria. The exclusion criteria included (a) literature published before 1980; (b) text not published in English; (c) articles not peer-reviewed; and (d) websites unrelated to non-pharmacotherapy, psychotherapy, depression, and cardiovascular disease.

Chapter 4

Results

The predominance of research investigating the effects of different forms of non-pharmacotherapy, particularly psychotherapy on mental health and depression, point to a reduction in depressive symptoms with mental and emotional counseling. Psychotherapy is also referred to as talk therapy, counseling, psychosocial therapy or, simply, therapy (Mayo Clinic, 2016). In a meta-analytic review of research, Kolovos, Kleiboer, and Cuijpers (2016) aimed to discover the effects of psychotherapy on both reducing symptom severity in depressed patients, as well as the effects of psychotherapy on quality-of-life (QoL), and mental and physical health as related to QoL. According to Kolovos et al. (2016), "quality-of-life (QoL) is a broad concept that comprises a range of life domains of the individual, such as social relationships, physical abilities, mental health functioning, role functioning and engagement in daily activities. Deficits in all these domains have been identified in people experiencing depressive symptoms." The researchers assessed 44 randomized controlled clinical trials comparing subjects with depression who received psychotherapy treatment with controls. Inclusion criteria consisted of subjects who were 18-years-or-older, research from randomized control trials comparing subjects with depression who received psychotherapy versus a control group where psychotherapy was not administered. Only studies where subjects were diagnosed with a depressive disorder through a structural clinical interview were used. Psychotherapy was defined as any intervention where the core element was verbal communication between the depressed subject and a therapist, or as a systematic psychological intervention in which the depressed participant worked independently on self-help measures such as with a book or website, while simultaneously receiving personal

support from a therapist (Kolovos et al., 2016). Quality-of-life is defined "as any patient-reported measure aiming to assess perceived health status, well-being or effective performance in daily life. These measures could provide a global (overall) score, or separate scores for different domains or components." Kolovos et al., (2016) included studies where QoL was centered on the mental and physical health of subjects. Mental health was defined as a personal satisfaction with the current psychological state, while the physical health component of studies was defined as "the perceived competence for performance and functioning in various everyday activities" (Kolovos et al., 2016).

The 44 studies that met inclusion and exclusion criteria encompassed a total of 5264 patients, with 2907 in the intervention group who received psychotherapy and 2357 patients in the control group without treatment. Of the 44 studies included in their research, 25 studies involved cognitive-behavioral therapy, mindfulness-based cognitive therapy, and coping with depression as forms of psychotherapy administered (Kolovos et al., 2016). Furthermore, researchers assessed quality-of-life as "life review in five studies (14%), problem-solving treatment in three studies (8%), acceptance and commitment therapy in three studies (8%) and interpersonal psychotherapy in two studies (5%)." The most common control condition for subjects was "care as usual" and this was included in 20 (45%) of the studies analyzed for data. Control conditions ranged from discussion groups, psycho-education, and a 20-minute educational video or placebo pill. Subjects received an average of 10 treatment sessions for depression.

According to Kolovos et al. (2016), results of their study indicated that psychotherapy for depression, mental health, and physical health reduced symptoms of depression and increased quality-of-life for most subjects. Thus, results of their study supported previous evidence

indicating a positive effect on depression, mental and physical well-being through psychotherapeutics. Moreover, Kolovos et al. (2016) concluded that "psychotherapy for depression is beneficial not only for depressive symptoms but also for quality-of-life. Overall, it can be concluded that psychotherapy has a positive impact on various domains of a patient's life, such as mental functioning, social and work-related relationships, level of discomfort and engagement in everyday activities." Patients who engaged in psychotherapy experienced greater improvements in QoL compared to control conditions. Additionally, the mental health component had the largest effect size when treated with psychotherapy. The smallest effect was seen in the physical health component, while there was only a moderate effect size for global QoL. Despite the smaller effect, physical health is an important predictor of cardiovascular health (Chaddha et al, 2016).

Researchers Pinheiro, Reshetnyak, Sterling, Richman, Kern and Safford (2019) used data from the national Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study to determine associations between baseline heart-related quality-of-life (HRQOL) and incident CVD events among adults with no history of stroke or heart disease. After their analysis of 1766 CVD events, Pinheiro et al. (2019) found that subjects who had scores of Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of less than 50, which range from 0 to 100, had a lower heart-related quality-of-life, while higher scores indicated better HRQOL. To further support this, higher self-reported PCS and MCS scores were significantly associated with a lower risk of cardiovascular disease in patients, while lower scores were indicative of a higher risk for cardiovascular disease, coronary artery disease, and stroke (Pinheiro et al., 2019).

Kolovos et al. (2016) acknowledge some limitations of their study. While there was only a small effect size of psychotherapy on physical health, they mention that only a few comparison studies were available discussing the effects of psychotherapy on physical health and they "lacked adequate power to detect small effect sizes. A larger number of studies would allow [the interpretation] of results with more confidence." Further research should be conducted on the effects of psychotherapy on patients with depression and their physical health (defined as the perceived competence for performance and functioning in various everyday activities) (Kolovos et al., 2016). Kolovos et al. (2016) state that QoL is inherently a subjective construct that could be perceived differently depending on the individual. Thus, it becomes difficult to measure the exact effects of psychotherapy on global QoL. Additionally, the research design used by Kolovos et al. (2016) did not allow researchers to determine causal or temporal relationships between QoL and symptoms of depression. Hence, "a longitudinal design with repeated measurements of QoL and depressive symptoms is needed to examine whether changes in depressive symptoms lead to changes in QoL or vice versa" (Kolovos et al., 2016). Kolovos et al. (2016) also acknowledge that their study only examined the short-term effects of psychotherapy on major depressive disorder, mental and physical health. Long-term studies should be encouraged to determine any further effects of psychotherapy on people with depression. While limitations of the study exist, psychotherapy is shown to be an effective treatment for people who experience both depressive symptoms and distress in their quality-of-life.

High rates of depressive disorders are found in primary care settings, where patients are receiving treatment (Nieuwsma, Trivedi, McDuffie, Kronish, Benjamin, & Williams, 2018). Despite the availability of extensive evidence and clinical guidelines that strongly encourage the

treatment of depression with both psychotherapy and pharmacotherapy, “medication is by far the most commonly utilized intervention in primary care settings” (Nieuwsma et al., 2018). However, primary care health professionals who treat patients with major depressive disorder continually try to integrate both psychotherapy and pharmacotherapy in treating patients for several beneficial reasons. According to Nieuwsma et al. (2018), integrating both psychotherapy and pharmacotherapy has multiple advantages over treatment with only one-or-the-other. “There are many patients who prefer psychotherapy to medication; there is a need to provide alternative treatments for patients who do not improve on or cannot tolerate antidepressant medication and there may be unique benefits from psychotherapy in terms of costs and relapse prevention” (Nieuwsma et al., 2018). One of the main obstacles in providing patients with non-pharmacotherapy for depression is the lengthy aspect of psychotherapy. Most patients who engage in psychotherapy for depression are required to participate in 12 to 20 weekly 1-hour sessions with a therapist and “is arguably still too intensive for reliable implementation in primary care settings” (Nieuwsma et al., 2018). Thus, it is important to recognize the time and resource constraints of traditional psychotherapies and determine whether brief psychotherapy sessions are as effective in relieving depression as the standard-duration psychotherapies (i.e., 12-20 sessions). In their article Nieuwsma et al. (2018) investigate whether brief sessions of psychotherapy of 8 or fewer sessions are efficacious for the treatment of depression. The authors conducted a systematic review of research investigating the effects of lengthy versus brief psychotherapy sessions for major depressive disorder. Particular attention was devoted to the “training received by providers delivering brief psychotherapies and the reporting of clinical outcomes beyond depression severity” (Nieuwsma et al., 2018). It is important to reiterate the strong positive bidirectional correlation between depression and CVD. Therefore, by reducing

the symptoms of depression in patients through short or long-term psychotherapy, we can further reduce the risk of cardiovascular disease.

After conducting a complex systematic review of the research available on MEDLINE (PubMed), Embase, and PsycINFO investigating standard versus brief psychotherapy for depression, a total of 2 systematic reviews and 15 randomized control trials met both inclusion and exclusion criteria (Nieuwsma et al., 2018). A total of 1716 patients encompassed all 17 research articles. Adults diagnosed with major depressive disorder (MDD), dysthymic disorder, or subthreshold (minor) depression in acute-phase treatment were included in the review. Studies that included subjects being treated with "cognitive-behavioral therapy (CBT) (including cognitive therapy and behavior therapy), interpersonal therapy (IPT), problem-solving therapy (PST), mindfulness-based cognitive therapy (MBCT), cognitive behavioral analysis system of psychotherapy (CBASP), dialectical behavioral therapy (DBT), functional analytic psychotherapy (FAP), acceptance and commitment therapy (ACT), or short-term psychodynamic therapy with ≤ 8 planned sessions were included in the review" (Nieuwsma et al., 2018). Research where subjects were treated with antidepressant medication (if the intervention was psychotherapy plus antidepressant) were included. Inclusion criteria for settings involved outpatient general medical or general mental health clinics. All included research measured depressive symptoms using a validated instrument which reported patient status at ≥ 6 weeks following randomization. Furthermore, subjects with treatment-resistant depression, postpartum depression, premenstrual dysphoric disorder, bipolar disorder, seasonal affective disorder, or double depression (i.e., MDD and dysthymia) were excluded from the review (Nieuwsma et al., 2018). Studies where subjects received the following interventions for depression were excluded: generic counseling, life review therapy, psycho-educational therapy, supportive

therapy, bibliotherapy, or Internet-based psychotherapies. Any study conducted outside of North America, Western Europe, New Zealand, or Australia were also excluded (Nieuwsma et al., 2018). There were no exclusion criteria for outcomes of brief psychotherapy.

Many of the studies used in Nieuwsma et al.'s (2018) review did not use a single type of instrument to measure depression severity. Therefore, Nieuwsma et al. (2018) calculated effect sizes for each study by "subtracting (at post-test) the average score of the control group from the average score of the experimental group and dividing the result by the pooled standard deviations (SDs) of the experimental and control groups." After assessing results of their meta-analysis, Nieuwsma et al., (2018) found that patients who engaged in 6 to 8 sessions of psychotherapy had reduced symptoms of depression (ES −0.42, 95% CI −0.74 to −0.10) as compared to participants receiving a control treatment. However, the effects of treatment were significantly different across all studies (Cochran Q=13.74, p=0.03, I2=56%). A limitation of the analysis of brief cognitive-behavioral therapy for depression was the small number of studies available at only 6—making it difficult for Nieuwsma et al. (2018) to detect publication bias. While only six studies using brief cognitive-behavioral therapy was a limiting factor, after correcting for confounding variables, Nieuwsma et al. (2018) found that 6 to 8 sessions of cognitive-behavioral therapy was significantly more effective in relieving symptoms of depression in patients compared to controls (ES −0.50, 95% CI −0.91 to −0.09). Furthermore, the single study investigating the effects of brief mindfulness-based cognitive therapy (MBCT) on depression "found 8 sessions of MBCT to be more efficacious than treatment as usual at reducing depressive symptoms at 8 weeks" (F=13.42, p=0.001) (Nieuwsma et al., 2018). According to Nieuwsma et al. (2018), "effect sizes for brief psychotherapy are modest but at present appear comparable to those observed in trials of antidepressant medications and of standard duration

psychotherapies." Moreover, for patients with severe depression, 16 sessions of psychotherapy were found to be more effective in reducing symptom severity than only 8 sessions (Nieuwsma et al., 2018).

There were several strengths and weaknesses of the Nieuwsma et al.'s (2018) meta-analytic review. The low number of available studies was a limiting factor in the strength of the conclusions drawn by the authors—that brief psychotherapy is as effective as standard psychotherapy for the treatment of depression. Also, psychotherapy for patients was administered by various types of health professionals including "psychologists, graduate students, nurses, general practitioners, and other allied health professionals who had received training and supervision specific to the intervention being conducted" (Nieuwsma et al., 2018). However, a varied type of professional intervention offered sparse details about the training received by counselors to provide therapy for patients, "meaning that the degree of training necessary to replicate studies' results is uncertain" (Nieuwsma et al., 2018). Furthermore, too few studies investigated the effects of brief psychotherapy for the long-term (6 months or more) treatment of depression. The subject population demographics were limited primarily to Caucasian, middle-aged females, which does not allow results to be transferable to other segments of the population. Finally, according to Nieuwsma et al. (2018) "the relatively few studies included in this review did not allow for stratified comparisons on important variables such as depression severity (i.e., mild, moderate, severe), treatment setting (e.g., mental health clinic, primary care), or augmentation of brief psychotherapy with medication." While strengths and weaknesses of their study do exist, Nieuwsma et al. (2018) still encourage the implantation of brief psychotherapy along with pharmacology for the treatment of major depressive disorder

in primary care settings, specifically noting the added benefits of talk therapy to medication in the treatment of mental health disorders.

As previously reflected in Nieuwsma et al.'s (2018) literature, another form of psychotherapy, cognitive behavior therapy (CBT), improves depressive symptoms in patients. Since depression and cardiovascular disease are strongly related, a randomized controlled trial by Turner, Hambridge, Baker, Bowman, and McElduff (2012) examined the influence of group cognitive behavior therapy versus brief intervention for depression in cardiac patients. In their study, a total of 57 community-dwelling cardiac patients who had a score of >13 on the Beck Depression Inventory-II received a single-brief psychotherapeutic intervention for depression. Following their brief session of psychotherapy, these patients were later block randomized to either six sessions of group cognitive behavior therapy (n=25) or no further intervention (n=32). All patients were reassessed for depression severity at 2, 6, and 12 months using the Beck Depression Inventory-II and the Hospital Anxiety and Depression Scale-Anxiety (HADS-A). The HADS-A assesses rates of depression and anxiety symptoms (Turner et al., 2012). Results of Turner et al.'s (2012) indicated significant improvements for the total group from baseline to 12 months follow-up. Turner et al. (2012) discovered no significant differences in cognitive behavior interventions or brief interventions on the BDI-II score, major rates of depression, or on the HADS-A score. While there was no difference between CBT and brief intervention for depression in cardiac patients, overall results indicated group psychotherapy reduced symptom severity in depressed patients. Furthermore, Turner et al. (2012) state that "non-response to depression treatment following acute myocardial infarction has been associated with increased cardiac morbidity." Therefore, cognitive behavior therapy for depressed cardiac patients is a

promising non-pharmaceutical intervention to prevent the progression of cardiovascular disease in depressed patients.

Cognitive behavioral therapy is one of the most common forms of psychotherapy used by mental health professionals to treat mental and emotional disorders, particularly major depressive disorder (Leuzinger-Bohleber et al., 2019). Much of the research available investigates the effects of psychotherapy on major depression and centers on cognitive behavioral therapy. Cognitive behavior therapists usually treat patients with depression through "problem analysis, goals, psychoeducation, rationale for treatment; behavioral activation, increasing pleasant activities; cognitive interventions to restructure basic assumptions, schemata; social skill training, problem-solving, stress management; maintenance, and relapse prevention" (Leuzinger-Bohleber et al., 2019). Moreover, previous studies investigating the mental health implications of short-term cognitive-behavior therapy have established it as an effective treatment for acute unipolar depression. Additionally, short-term psychodynamic psychotherapy (PAT) was found equally effective compared to short term CBT and other psychotherapies (Leuzinger-Bohleber et al., 2019). A more recent controlled, single-blind, multicenter, 4-arm study by Leuzinger-Bohleber et al. (2019) was first to compare the effectiveness of long-term cognitive-behavioral therapy and long-term psychoanalytic therapy on chronically depressed patients and the effects of preferential or randomized allocation on outcomes.

A total of 252 adult males between the ages of 21 and 60 years-of-age who were gathered from 4 study centers in Germany (Frankfurt, Mainz, Berlin, and Hamburg) met the inclusion and exclusion criteria set forth by Leuzinger-Bohleber et al. (2019). All of these men had been suffering from either major depression, dysthymia, or double depression for at least 12 months or more. Dysthymic disorder (DD) is defined as a mild or moderate form of chronic depression but

those diagnosed with dysthymia still meet the criteria for a major depressive episode or double depression occurring at some point in their lives (Klein, Shankman, & Rose, 2008). Double depression is a complication of dysthymia in which the individual experiencing mild chronic depression succumbs to the full syndrome of major depressive disorder later in life, usually a result of not seeking treatment (WebMD, 2017). Furthermore, only subjects with a depression severity score of >9 on the clinician-rated Quick Inventory of Depressive Symptoms (QIDS), and a score of >17 on the Beck Depression Inventory II (BDI-self-report), and those who gave informed consent were asked to participate. Leuzinger-Bohleber et al. (2019) gave subjects the ability to choose whether to be treated with long-term cognitive-behavioral therapy or long-term psychoanalytic therapy, or were assigned to treatment randomly. Patients taking antidepressant medication were only included in the study if they were taking the medication for at least 4 weeks (Leuzinger-Bohleber et al., 2019). A total of 73 psychoanalytic therapists were recruited to provide counseling to patients. Psychoanalytic therapists were trained in their discipline by engaging in workshops centered on the empirically validated psychoanalytic manual for the treatment of chronic depression. Additionally, psychoanalytic therapists were taught to "uncover and modify the unconscious idiosyncratic fantasies and conflicts due to developmental deficits and traumatizations underlying chronic depression…manifested in dreams, current object relationships, fantasies leading into psychic retreat) and worked through the 'here and now' of the transference relationship, aiming to change the psychic structure" of the patient (Leuzinger-Bohleber et al., 2019). Both psychoanalytic therapists and state-licensed cognitive-behavioral therapists were required to have at least three years of previous clinical practice. Leuzinger-Bohleber et al., (2019) refer to their research as the Long-term Psychotherapies for Chronically Depressed Patients (LAC) study.

To measure patient adherence to both psychoanalytic therapy and cognitive-behavioral therapy, Leuzinger-Bohleber et al., (2019) used the Comparative Psychotherapy Process Scale (CPPS) and analyzed randomly selected audiotapes of therapy sessions. Audiotapes were assessed for type of therapy given and for interrater reliability which was satisfactorily high with an intraclass correlation coefficient score (ICC) of >.85. The Beck Depression Inventory II (BDI) and the (clinician-rated) QIDS were used to measure the main outcomes of the study. Data results were presented as follows: "over the first year, the average (total) BDI declined from 32.1 by 12.1 points and 17.2 points after 3 years. BDI overall mean effect sizes increased from d ¼ 1.17 after 1 year to d ¼ 1.83 after 3 years. Full remission rates for BDI increased from 34% to 45% after 3 years. The average QIDS-C declined by 6.4 points over the first year and by 8.5 points over 3 years. The QIDS-C overall effect sizes increased from d ¼ 1.56 to d ¼ 2.08, and full remission rates rose from 39% after 1 year to 61% after 3 years" (Leuzinger-Bohleber et al., 2019). Thus, Leuzinger-Bohleber et al.'s (2019) study results suggest a significant reduction in depressive symptoms after long-term treatment with psychoanalytic and cognitive-behavioral therapy for patients suffering from chronic depression. Also, patients who were treated with their preferred form of psychotherapy did not achieve better outcomes than patients who were randomly allocated to their form of treatment therapy.

There are various weaknesses in the LAC study by Leuzinger-Bohleber et al. (2019). One of the main weaknesses involves the all-male study population, preventing the application of results to females. The study population also included only subjects gathered from different locations in Germany. Thus, cultural or ethnic variations are not accounted for in Leuzinger-Bohleber et al.'s (2019) study and further research on the effects of long-term psychotherapies on chronic depression should be conducted on diverse groups. Since two-thirds of the study

population had a therapeutic preference, the randomization arm for the random allocation to therapy was not strong enough to determine true power. Further, the study population included severely ill patients considered "difficult-to-treat," who had experiences with severe and cumulative childhood trauma, primarily emotional neglect, which may lead to an increased likelihood of relapse into depression. Moreover, because the participants were severely ill patients, medication could not be stopped or modified for ethical reasons. According to Leuzinger-Bohleber et al., (2019), "despite these limitations, the conclusion of this study is that psychoanalytic long-term psychotherapy, as well as cognitive-behavioral long-term psychotherapeutic treatments, help chronically depressed patients to achieve a sustained reduction of depressive symptoms and to substantially improve the remission rates." Results of the study indicated no significant difference between psychoanalytic therapy and cognitive-behavioral therapy in reducing symptoms of depression. While Leuzinger-Bohleber et al.'s (2019) did not investigate the relationship between depression and cardiovascular disease in patients, or whether patients with depression were also diagnosed with cardiovascular disease, previous research strongly suggesting the interrelationship between depression and CVD does point to the benefits of psychotherapy for both disease states. Additionally, the significant improvements in the severity of depressive symptoms in patients using psychoanalytic long-term psychotherapy and cognitive behavior therapy again highlights the underlying bidirectional relationship between depression and cardiovascular disease—a decrease in depression likely correlates to a decreased risk for cardiovascular disease through treatment with various forms of psychotherapy.

Another randomized control trial conducted by Nakagawa et al. (2017) aimed to determine the effectiveness of supplementary cognitive-behavioral therapy for pharmacotherapy-

resistant depression. In their rationale, Nakagawa et al. (2017) allude to the difficulty in treating all depressed patients with pharmacotherapy, since "antidepressant medication is efficacious in the treatment of depression, but not all patients improve with antidepressant medication alone." Additionally, "it is estimated that only a third of patients fully respond to the initial course of antidepressants and only a quarter to the second course. The sizable proportion of patients who fail to respond to pharmacotherapy is considered to have treatment-resistant depression" (Nakagawa et al., 2017). A plethora of research suggests that cognitive-behavioral therapy is equally effective for depression as antidepressant therapy alone and combining cognitive-behavioral therapy and antidepressant therapy is even more effective (Nakagawa et al., 2017). While there is literature supporting combination therapy for the treatment of depression, there is a lack of research focused on combination therapy on pharmacotherapy-resistant patients suffering from depression and cardiovascular disease.

Nakagawa et al.'s (2017) research consisted of a 16-week assessor-masked randomized control trial with a 12-month follow-up that ran from September 2008 to December 2014. The subject population included adult outpatients between the ages of 20 and 65 years who had pharmacotherapy-resistant depression, and were taking antidepressant medication for at least 8 weeks. Subjects were also evaluated for the GRID-Hamilton Depression Rating Scale, the Maudsley Staging Method for treatment-resistant depression and were assessed for meeting the DSM-IV criteria for major depressive disorder. Only subjects with a score of ≥ 16 on the GRID-Hamilton Depression Rating Scale, a score of ≥ 3 on the Maudsley Staging Method for treatment-resistant depression scale, and those who met DSM-IV criteria for major depression were included in the study. A total of 80 participants seeking psychiatric specialty care were randomly assigned to two groups, those who would receive cognitive-behavioral therapy with

treatment as usual (TAU) or those who would receive TAU alone (antidepressant medication). The subjects were gathered from two study sites: a university teaching hospital and a psychiatric hospital located in Tokyo, Japan. Additional inclusion criteria consisted of having major depressive disorder as explained by the DSM-IV without psychotic features explained by the DSM-IV-TR Axis I Disorders Patient Edition. Exclusion criteria included any other DSM-IV Axis diagnosis other than major depressive disorder, manic or psychotic episodes, and alcohol or substance use disorder. Any subject with any form of anti-social personality disorder, serious and imminent suicidal ideations, organic brain lesions, or major cognitive deficits, as well as any serious or unstable medical conditions were excluded from the study. Additionally, subjects who have received cognitive-behavioral therapy in the past or had already attended at least 8 or more CBT sessions were excluded. Finally, subjects who were unlikely to adhere to at least 8 sessions of cognitive-behavioral therapy for the entirety of the study period were also excluded (Nakagawa et al., 2017).

Participants in the CBT group were offered sixteen individual sessions that lasted 50 minutes that were scheduled weekly. Some subjects were offered an additional four sessions if "deemed clinically appropriate by the therapist" (Nakagawa et al., 2017). The therapists that counseled patients with cognitive-behavioral therapy followed guidelines and procedures set forth by the CBT Manual for Depression, which includes adaptations for Japanese culture and certain characteristics of Japanese patients, including "their emphasis on interpersonal relationships and consideration of family as an essential part of treatment" (Nakagawa et al., 2017). There were a total of four psychiatrists, one clinical psychologist with a master's degree, and one psychiatric nurse who provided cognitive-behavioral therapy to participants. The therapists were trained in cognitive-behavioral therapy for an average of 2.1 years and had

treated an average of 12.5 patients prior to the study. Training in cognitive-behavioral therapy included a two-day intensive workshop and two-hour onsite group supervision sessions every two weeks from a cognitive-behavioral therapy supervisor. Also, therapists were assessed for following procedures and guidelines using the Cognitive Therapy Rating Scale, in which all therapists passed with a score of > 40 (Nakagawa et al., 2017). Patients who maintained treatment, as usual, underwent medication management and received education on medication dosage, schedules, reviews of the positive adverse side-effects, and were given supportive guidance from their therapists. Depressive symptoms were monitored using the Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) and was conducted during each visit. Pharmacotherapy was not restricted in any manner, however, "treatments were in line with practice guidelines for depression care" (Nakagawa et al., 2017). Furthermore, the seven therapists assigned to the study evaluated subjects for medication every two weeks for 10-15 follow up sessions. All subjects in the treatment-as-usual group were not provided any form of cognitive-behavioral therapy as an intervention for depression during the entire study period. Subjects in the treatment-as-usual group with cognitive-behavioral therapy were treated for 16 weeks. Following the 16-week period, subjects were "assessed at 6 time points; baseline (at randomization); 8 and 16 weeks post-randomization; and 3, 6, and 12 months after the end of the 16-week intervention" (Nakagawa et al., 2017).

Nakagawa et al.'s (2017) analysis of the data presented at the completion of their study showed beneficial outcomes for the alleviation of depressive symptoms when adding cognitive-behavioral therapy to antidepressant medication for the treatment of major depressive disorder. Moreover, the alleviation of depressive symptoms at the completion of 16-weeks of treatment was greater in the cognitive-behavioral therapy group than in the treatment as usual group and

the least squares mean changes in GRID-HDRS17 was −12.7 vs −7.4, respectively. The between-group mean difference was significant as well at −5.4; 95% CI, −8.1 to −2.6; P < .001. According to Nakagawa et al. (2017), "the beneficial effects of CBT were maintained over the 12-month follow-up and were confirmed at 3 months (−13.2 vs −9.5; difference = −3.7; 95% CI, −6.4 to −0.9; P = .01), at 6 months (−14.9 vs −11.5; difference = −3.4; 95% CI, −6.2 to −0.6; P = .02), and at 12 months (−15.4 vs −11.0; difference = −4.4; 95% CI, −7.2 to −1.6; P = .002)." Interestingly, subjects allocated to the cognitive-behavioral group were 2.4 times more likely to have a response to treatment at 16-weeks in comparison to the treatment-as-usual group, while the benefits of cognitive-behavioral therapy in conjunction with antidepressant medication were confirmed at 3, 6 and 12 months.

The study by Nakagawa et al. (2017) had several strengths and weaknesses. An important strength of the study was the high rate of cognitive-behavioral therapy completion at 97.5% and a low dropout rate of 8.8% which translates to a highly motivated subject population. Meanwhile, one limitation presented here is that the highly-motivated nature of participants makes it difficult to generalize these results to the average population. Also, the small sample size of only 80 patients of Japanese origin does not allow for the generalization of results to other population demographics. Nakagawa et al. (2017) state that the experience levels of the therapists had a graded effect on the degree of alleviation of depressive symptoms in participants, i.e., the psychiatrists with more education and experience had more beneficial effects on patients. The researchers state that "the possible contribution of the variance of non-protocol–based therapeutic effects among different therapists should be acknowledged. Patients with difficult-to-treat depression were reported to show differences in CBT response that were associated [the] with therapists' experience levels." For this reason, a standardization of training

and education for the treatment of depression with cognitive-behavioral therapy, with "supervision and technical assistance, is crucial for implementing evidence-based CBT" and psychotherapeutics in general, and should be achieved by professionals responsible for counseling patients suffering from major depression (Nakagawa et al., 2017). Another limitation of Nakagawa et al.'s (2017) study is researchers were unable to fully control antidepressant medication and antidepressant medications were similar but not all the same. Thus, different types of antidepressants may affect patients differently. Additionally, since there was no control group for patients receiving cognitive-behavioral treatment alone, the effects of cognitive-behavioral therapy cannot be established. While strengths and limitations of Nakagawa et al.'s (2017) study do exist, a combination approach of psychotherapeutics and pharmacotherapy, specifically cognitive-behavioral therapy and antidepressants, is beneficial to patients with major depressive disorder. Furthermore, for patients with comorbid depression and cardiovascular disease, cognitive-behavioral therapy may be beneficial for both health conditions.

Cognitive-behavioral therapy has been established as an effective treatment for patients suffering from major depression (Hensley, Nadiga, & Uhlenhuth, 2004). Researchers Hensley et al. (2004) aimed to further investigate the effects of cognitive-behavioral therapy for the long-term treatment and prevention of major depressive disorder, and its effectiveness as compared to traditional medical treatment using tricyclic antidepressants. According to Hensley et al. (2004), "few clinicians expect acute treatment of depression with antidepressant medication to prevent long-term relapse of the illness, some practitioners of cognitive therapy report long-term effectiveness in preventing relapse after short-term treatment." Thus, Hensley et al. (2004) reanalyzed follow-up using intent-to-treat principles to assess the long-term effects of the acute treatment of depression treated with cognitive therapy. A total of five trials published between

1981 and 1992 that compare cognitive-behavioral therapy to tricyclic antidepressants met the inclusion and exclusion criteria. Results of the meta-analysis indicated that cognitive-behavioral therapy offers a more beneficial long-term treatment of major depression as compared to tricyclic antidepressants (Hensley et al., 2004). Given the relevance of psychological well-being to promoting cardiovascular health, cognitive behavior therapy for depression likely plays a dual role in reducing the risk for CVD.

Other Non-Pharmaceutical Therapies for Mental and Cardiovascular Health

There is a lack of research on the effects of psychotherapy on comorbid depression and cardiovascular disease. However, several studies do investigate the influence of other forms of non-pharmacotherapy for cardiovascular health and subsequently mental health. Such therapies include meditation, exercise therapy, acupuncture, and musical therapy. The current research looking into the possible links between meditation and heart disease focus on the physiological response to stress, smoking cessation, blood pressure reduction, insulin resistance and metabolic syndrome, endothelial function, inducible myocardial ischemia, and the primary and secondary prevention of cardiovascular disease.

A study by Levine et al. (2017) aimed to discover the impact of meditation on cardiovascular risk reduction. According to Levine et al. (2017), the quality of data on current research is only satisfactory and the availability of studies is low. Education, a modification in lifestyle behaviors, and pharmaceutical interventions have decreased the prevalence of cardiovascular risk factors in the United States and in the developed world. As indicated in Turner et al.'s (2012) study, cardiac patients receiving group cognitive behavior therapy who reported excess alcohol consumption and smoked cigarettes and "who did not meet remission criteria at 12 months had significantly higher baseline Beck Depression Inventory-II scores,

more visits to health professionals in the 12 months prior to baseline and were more likely to smoke and/or drink alcohol over recommended levels at baseline. Furthermore, despite the improvements described by Levine et al. (2017), cardiovascular disease remains the leading cause of death around the world. The practice of meditation dates back to 5000 B.C. and is a common practice in both Buddhist and Hindu cultures, and can be found in historic texts of Christianity, Judaism, and Islam. Levine et al. (2017) state that "in the traditional context, meditation refers to a family of mental practices that are designed to improve concentration, increase awareness of the present moment, and familiarize a person with the nature of their own mind. In a more general and contemporary context, meditation can be categorized as primarily focused attention, mindfulness, loving kindness and compassion, or mantra repetition, although there is usually an overlap between the focuses." According to the National Health Interview Survey, approximately 8% of Americans engage in some form of meditation practice, and between 14% and 24% of patients with cardiovascular disease report taking part in some form of mind-body therapy, while about 2% to 3% of cardiac patients engage in some sort of meditation therapy (Levine et al., 2017). One of the major advantages of meditation is its low cost. Compared to a $200 billion-dollar U.S. healthcare expense on patients with CVD each year (which is expected to double or triple in the next few decades), meditation can be easily incorporated into one's daily life through learned publications, internet sources, audio media, as well as inexpensive courses (Levine et al., 2017). For this reason, meditation can be a cost-effective treatment option for depression and lowering the risk of cardiovascular disease, and may be combined with conventional medical practice using pharmacology when appropriate for the patient. The following study by Levine et al. (2017) was commissioned by the American

Heart Association to systematically review the association between meditation and cardiovascular disease.

To further the discussion on meditation and health, it is imperative to understand the neurophysiological and neuroanatomical influences of meditation. According to Levine et al. (2017), over two decades of scientific research from over twenty universities has suggested the profound ability for meditation to alter the human brain. While "most forms of meditation engage regions in the brain that regulate attention and emotion…the adult brain can undergo changes through a process called neuroplasticity, which may include development of new circuits ("rewiring") and/or neurons" (Levine et al., 2017). Various forms of sitting meditation also have an effect on neural circuits that include "different sectors of the prefrontal cortex and anterior cingulate cortex, the insula, and the midline regions that are important in default mode function" (Levine et al., 2017). Furthermore, studies that examined loving-kindness and/or compassion meditation show alterations in the subcortical circuits of the brain which have a direct influence on human emotional processing, including the amygdala and the ventral striatum. In addition, research on the impact of meditation on the brain has also shown the beneficial effects of meditation on the human physiological basal state, physiological responses, and cardiovascular risk (Levine et al., 2017). However, the reader must be informed that these studies were limited in the number of participants involved which could reduce the significance of the data presented. Also, different types of meditation will pose different types of neurological, physiological, and psychological responses in the patient and should be further investigated.

In their research, Levine et al. (2017) used PubMed, Google, and Google Scholar to search for articles linking the effects of meditation on cardiovascular disease. Search terms

included meditation, stress, blood pressure, hypertension, smoking, tobacco use, insulin resistance, metabolic syndrome, atherosclerosis, endothelial function, myocardial ischemia, primary prevention, and secondary prevention. The review was limited to practices of sitting meditation and did not include any type of practice that consisted of both mental and physical practices, i.e. tai-chi, qigong, and yoga, as research shows physical activity reduces the risk of cardiovascular disease and this would be confounding to the data. Levine et al. (2017) isolated studies that involved quality information on meditation and cardiovascular risk reduction; meditation and the psychological, psychosocial, and physiological responses to stress; the effects of meditation on blood pressure, insulin resistance, and metabolic syndrome; and the effects of meditation on subclinical atherosclerosis and endothelial function.

Numerous studies were found by Levine et al. (2017) that investigated the link between meditation, cardiovascular risk reduction, and the psychological, psychosocial, and physiological human response to stress during meditation practice. Most of the studies suggested the amelioration of the perceived levels of stress, mood, anxiety, depression, quality of sleep, and improved overall wellbeing by subjects following meditation therapy. These studies were exclusive of randomized controlled trials. However, only a few of the studies included participants with cardiovascular disease. One of the studies examining 60 patients from a private cardiology clinic found that "those randomized to 8 weeks of mindfulness-based stress reduction (primarily using meditation techniques) had significantly lower perceived stress and anger than a comparison control group" and researchers found that meditation strongly improved overall quality-of-life (Levine et al., 2017). Hence, the psychological component of these studies is important to consider when discussing the interrelationship between psychotherapy (meditation),

depression, and cardiovascular disease. Additionally, this association further advocates the beneficial relationship between positive thoughts and physical wellbeing.

Meditation not only improves psychological, psychosocial, and physiological health, but a few high-quality, randomized studies have found it also lowers blood pressure. According to Levine et al. (2017), "a pilot study of 83 predominantly hypertensive blacks randomized to a mindful meditation program or control social support group, [where] a 11/4 mm Hg decrease in systolic/diastolic blood pressure was observed in those randomized to 8 weeks of treatment and an analysis adjusted 22/17 mm Hg difference in blood pressure between the 2 groups at follow-up." Strengths of the study include its 100% data ascertainment, over 80% compliance rate from patients at visit to the clinic, and "measured blood pressure with an unattended manual device (a rigorous protocol with measurements 7–15 mm Hg lower than typical office readings)" (Levine et al., 2017). Furthermore, another randomized study of 201 African American men and women "with angiographically documented coronary artery disease randomized to transcendental meditation or health education, after 5.4-year follow-up found a 4.9 mm Hg lower systolic blood pressure, [one] of numerous secondary study end points, in those randomized to transcendental meditation than in those randomized to health education, primarily because of an increase in blood pressure in the health education group" (Levine et al., 2017). The relationship between blood pressure and the increased risk of cardiovascular disease has been well-established in the medical community. Research suggesting the association between meditation (affecting the mind and body) to a reduction in blood pressure strengthens the claim that therapies for the mind have an influence on our physical health, particularly when discussing heart health. Furthermore, a 2013 American Heart Association (AHA) scientific statement on non-pharmaceutical approaches to lowering blood pressure concluded that "transcendental

meditation modestly lowers blood pressure and that its use may be considered" (Levine et al., 2017). In this announcement, the AHA also made note of the insufficient number of high-quality studies investigating other forms of meditative therapies and their effects on lowering blood pressure (Levine et al., 2017). One limitation of the research available between blood pressure and meditation is the average completion rate (percent of patients who completed all training and post-test) for the studies, which was only 63% (Levine et al., 2017). Further research on the effects of meditation on blood pressure should be investigated to increase the strength of any positive association between the two variables. Furthermore, another smaller scale study looking at the relationship between blood pressure and meditation found neurophysiological changes in patients with hypertension and chronic kidney disease. A total of 15 participants with hypertension and chronic kidney disease were evaluated following engaging in mindful meditation. Patients reported a decrease in muscle sympathetic nervous activity and blood pressure. However, long-term effects of meditation on hypertension and chronic kidney disease could not be established (Levine et al., 2017). The study was limited by its small sample size.

Researchers have also attempted to discover whether a correlation exists between meditation and metabolic syndrome. Metabolic syndrome is a risk factor for diabetes mellitus and cardiovascular disease—thus the potential for meditation to reduce the conditions and symptoms related to metabolic syndrome is valuable for also reducing the risk for cardiovascular disease. One study with a total of 103 subjects who were diagnosed with coronary artery disease were randomized into two groups—a control group in which patients received health education, or a group that participated in transcendental meditation. The group that engaged in transcendental meditation experienced improved insulin resistance (Levine et al., 2017). The study also evaluated the effects of yoga, and a vegetarian diet on metabolic syndrome. This

multimodal approach to the study limited its conclusions as yoga and a vegetarian diet are confounding variables that most likely have an effect on metabolic syndrome. Thus, this study was limited by its multimodal experimental setting and moderate sample size.

The association between metabolic syndrome, cardiovascular disease, and non-pharmacotherapy is novel and a small number of studies exist that delve into this topic. Thus, the medical and scientific community should encourage further research on the effects of non-pharmacotherapy on metabolic syndrome—a strong risk factor for cardiovascular disease.

In their article, researchers Levine et al. (2017) also discuss the association between meditation and subclinical atherosclerosis. Atherosclerosis is a condition in which the arteries have become hardened by the buildup of plaque overtime, leading to an increased risk for cardiovascular disease since blood circulation is compromised (Levine et al., 2017). Levine et al. (2017) found only one study investigating the effects of meditation on the progression of atherosclerosis. A total of 138 hypertensive African Americans were randomized to either a group partaking in transcendental meditation or a control group in which participants were placed in a health education program. Subjects in both the transcendental meditation group and the control group were followed for an average of 7 months. Data on carotid intimal thickness was collected during the 7-month follow-up (Levine et al., 2017). One limitation of the study was the high attrition rate of 57% of patients who did not complete the studies total duration. With those subjects who completed the study, the meditation group showed carotid intimal thickness regression, “whereas progression occurred in the control group, with the difference between the 2 groups being statistically significant” (Levine et al., 2017). Therefore, researchers concluded that transcendental meditation had positive effects on atherosclerosis and thus may reduce the risk for cardiovascular disease (Levine et al., 2017). Another limitation of the study

to consider is the study population demographics. Since only African American men were included, results of the study cannot be applied to women or people of other races or ethnicities. Moreover, Levine et al. (2017) found another study of 57 healthy adults aged 65 or older. Participants were randomized to one of three interventions: "a transcendental meditation program that also included diet, exercise, and vitamin treatment; a diet/exercise/vitamin arm without the meditation component; or a usual care arm" (Levine et al., 2017). After one year of follow-up, the group who engaged in meditation presented with a reduction in carotid intimal thickness which was not observed in the other two intervention groups. The multimodal study design is a limiting factor of the study since the meditation group also included a healthy diet plan, exercise, and vitamin treatment. A reduction in intimal carotid artery thickness could be a result of diet, exercise, and the vitamin regimen independently, or a result of the combination of treatment modalities.

Inducible myocardial ischemia is another important cardiovascular condition to consider for treatment with non-pharmacologic techniques. Inducible myocardial ischemia occurs when blood flow to the heart is reduced, which prevents the heart muscle from receiving appropriate levels of oxygen (Mayo Clinic, 2019). Reduced blood flow to the heart is usually a result of a partial or complete blockage of the heart's arteries. Serious complications of inducible myocardial ischemia include an increased risk for heart attack, irregular heart rhythm, or heart failure (Mayo Clinic, 2019). While inducible myocardial ischemia significantly increases the risk for cardiovascular complications and even death, a lack of studies are available that investigate the influence of non-pharmacotherapeutics on myocardial ischemia. However, a study dating back to 1996 gathered 21 subjects with coronary artery disease. According to Levine et al. (2017), "7.6 months of transcendental meditation led to significant increases in

exercise duration (15%) and maximum work load (12%) compared with wait-listed controls, as well as lower rate-pressure products at given workloads and significantly delayed onset of ST depression." ST depression is a type of finding on an electrocardiogram in which the trace in the ST segment is abnormally low below the baseline and "ST depression is associated with acute coronary syndromes (ACS)—both acute ischemia and acute infarction; this electrocardiographic pattern, however, may also be found in patients with non-ischaemic events, such as left bundle branch block (LBBB), left ventricular hypertrophy (LVH), and those with therapeutic digitalis levels" (Pollehn, Brady, Perron, & Morris, 2002). Furthermore, another study conducted in 1983 assessed 43 patients with ischaemic heart disease that took a combination treatment approach for CVD. Treatment for these subjects combined stress management (meditation and stretching/relaxation exercises) and a vegan-based diet. Patients were analyzed after 24 days of multimodal therapy. Results of the study indicated a 44% increase in exercise duration, 55% increase in total work, and improved exercise ejection fraction and regional wall motion, "whereas no significant changes occurred in the control group" (Levine et al., 2017). Limitations of the study included the small sample size and the confounding variables presented by the multimodal approach to treatment. Thus, meditation alone cannot be independently deemed responsible for the improved changes in patients receiving treatment, as stretching, relaxation techniques, and a vegan diet may all lead to improvements in cardiovascular patient outcomes.

Levine et al.'s (2017) meta-analytic review also looked into research on the effects of meditation on the primary prevention of cardiovascular disease. According to the authors, recent Cochrane reviews have "concluded that no properly conducted randomized, controlled trials have assessed its role in the primary prevention of cardiovascular mortality or nonfatal primary

end points. This is largely because the relevant studies are small, with short-term follow-up and carried out in predominantly healthy participants" (Levine et al., 2017). However, a systematic review of randomized controlled trials investigating the link between meditation and the primary prevention of cardiovascular disease found that various non-pharmacotherapies including meditation, yoga, and a healthy diet were associated with improvements in physical and mental quality-of-life, depression and anxiety, and systolic and diastolic blood pressure—all of which have been shown to reduce the risk of cardiovascular disease in patients. Thus, while there is a paucity of research available delving into the relationship between meditation and CVD, it can be stated with confidence that cardiovascular health and psychological health are interrelated and a multimodal approach using both conventional and non-pharmaceutical therapies for their treatment is beneficial for overall quality-of-life.

The scientific and medical communities agree that the benefits of physical exercise are numerous for physiological and psychological health, as well as for the overall quality-of life. A study by Knapen, Vancampfort, Moriën, and Marchal (2014) investigated the influence of exercise therapy on mental and physical health on patients with major depression. According to Knapen et al. (2014), "depression is associated with a high incidence of co-morbid somatic illnesses, especially cardiovascular diseases, type 2 diabetes and metabolic syndrome." Additionally, "depressed persons have approximately a two-fold increased risk of having or developing cardiovascular disease. Further, after a cardiovascular event, the risk of onset of depression is increased, resulting in poorer cardiovascular outcomes. Metabolic syndrome, a constellation of cardiovascular risk factors including (abdominal) obesity, hypertension, dyslipidemia and hyperglycemia, has been suggested to be one possible pathway linking

depression and cardiovascular disease" (Knapen et al., 2014). Again, the link between depression and cardiovascular disease is strongly suggested.

Moreover, research has shown a strong connection between neuropsychiatric disorders, particularly major depression, and type II diabetes. According to Lyra e Silva, Lam, Soares, Munoz, Milev, and De Felice (2019), evidence shows that type II diabetes increases the risk of developing dementia, neuropsychiatric and mood disorders and "evidences of the involvement of insulin signaling on brain mechanisms related to depression indicates that insulin resistance, a hallmark of type 2 diabetes, could develop in the brains of depressive patients." Some studies show a bidirectional relationship between depression and type II diabetes and a recent report indicated that the severity of depression in children predicted the future development of insulin resistance. Furthermore, the more severe the insulin resistance detected in depressed obese youth, the more significant the symptoms of depression as well as the dysfunction of the anterior cingulate cortex-hippocampal motivational network (Lyra e Silva et al., 2019). Recent post-mortem analysis of the brain of patients who were suffering from diagnosed mental illness showed a correlation between "gene expression of proteins involved with both the dopaminergic system and insulin signaling, supporting the idea that insulin could regulate the dopaminergic response" (Lyra e Silva., 2019). To further elucidate the connection between insulin resistance and depression, Papazoglou et al. (2011) suggest that several hormones and neurotransmitters in the brain regulate the action of insulin in the body. The neurotransmitter serotonin (5-HT) is of particular importance for the control of food intake and energy homeostasis, as well as for the alleviation of mood, sleep, satiety (Papazoglou et al., 2011; Shabbir et al., 2013). Furthermore, according to Shabbir et al. (2013),

> "the serotonin precursor, tryptophan, can readily pass through the blood-brain barrier. Tryptophan is converted to 5-HT by tryptophan hydroxylase and 5-HTP decarboxylase, respectively, in the presence of pyridoxal phosphate, derived from vitamin B6. Hence diets poor in tryptophan may induce depression as this essential amino acid is not naturally abundant even in protein-rich foods. Tryptophan-rich diet is important in patients susceptible to depression such as certain females during pre and postmenstrual phase, post-traumatic stress disorder, chronic pain, cancer, epilepsy, Parkinson's disease, Alzheimer's disease, schizophrenia, and drug addiction."

From this research, the relationship between insulin resistance, depression and mood, sleep, and cardiovascular disease is further highlighted, and additional research between these connections should be investigated in the future.

Researchers Knapen et al. (2014) conducted a meta-analytic review of randomized control trials from the *Cochrane Collaboration* that investigated the effects of exercise therapy or no treatment on patients with major depression. A total of four studies met inclusion and exclusion criteria set forth by Knapen et al. (2014). The researchers wanted to answer specific questions regarding exercise therapy for depression including whether exercise is more effective than no treatment for depression; whether exercise is more effective than antidepressant medication for depression; is exercise more effective than psychological therapies or other nonmedical treatments for depression; and how patients accept exercise for the treatment of depression (Knapen et al., (2014). Inclusion criteria involved subjects diagnosed with major depression who were at least 18-years-old and patients had to be engaging in physical exercise that met the criteria for the definition of "exercise." After a review of the meta-analytic reviews

available that fit the inclusion and exclusion criteria set forth by Knapen et al. (2014), researchers pinpointed four articles matching their interests.

General results of Knapen et al.'s (2014) meta-analysis concluded that exercise is an effective non-pharmaceutical treatment for depression. Moreover, in patients with mild to moderate depression, exercise was as effective for the reduction of depressive symptoms as antidepressant medication (Knapen et al., (2014). Not only was exercise found to be an effective treatment for patients with major depression, but also "exercise therapy also improves physical health (e.g. metabolic syndrome), body image, and patient's coping strategies with stress, quality-of-life, and independence in activities of daily living in older adults" (Knapen et al., 2014). A more recent meta-analysis including 18 reviews with 5531 subjects found that metabolic syndrome occurs frequently in depressed patients with an average of 30.5% percent of those suffering from major depression also suffering from metabolic syndrome. It is important to reiterate the key understanding that the cluster of conditions that metabolic syndrome comprises of, all increase the risk for cardiovascular disease. Furthermore, Knapen et al. (2014) found that the relative risk for metabolic syndrome in patients with depression was 1.5 times higher than the general population—with no difference found between incidence rate in men and women, or age in the lifespan. Thus, physical exercise is indicated in the treatment of both depression and cardiovascular disease, as well as in reducing the risk factors associated with both conditions.

Knapen et al. (2014) located another meta-analytic review on the bi-directional relationship between metabolic syndrome and major depression. The meta-analysis concluded that metabolic syndrome is an independent risk factor major depression and patients with metabolic syndrome have a higher relative risk to develop clinically diagnosed depression (OR ¼

2.18) than those who do not suffer from metabolic syndrome (Knapen et al. (2014). According to Knapen et al. (2014), "the positive bi-directional longitudinal association between depression and metabolic syndrome means that depression is causing metabolic syndrome and vice versa. This association suggests a possible pathophysiologic overlap. More specifically, elevated cortisol, epinephrine, and norepinephrine secretion due to hyperactivity of the hypothalamic–pituitary adrenal (HPA) axis, (pro)-inflammatory processes, oxidative stress, autonomic nervous system dysregulation, and insulin resistance are all interacting biological mechanisms that may mediate the association between depression and metabolic syndrome." The researchers also conclude that depression and metabolic syndrome are associated with an increased risk of mortality and morbidity, most likely the result of an increased risk for cardiovascular disease and diabetes mellitus type II. Thus, exercise therapy also plays a dual role in the improvement of both depression and cardiovascular disease in patients suffering from either one or both health conditions.

Acupuncture is another form of non-pharmacotherapy that has become more popular for the treatment of a variety of health conditions, including depression and cardiovascular related disorders. A case study by Lin, Qin, and Wang (2018) discusses the effects of Traditional Chinese medicine (TCM) acupuncture combined with musical therapy for the treatment of post-stroke depression (PSD). In the United States, post-stroke depression is typically treated using western medical practices mostly consisting of a prescription medication regimen that reportedly increases the pain and suffering of patients due to adverse side-effects (Lin et al., 2018). For this reason, researchers Lin et al., (2018) aimed to discover the influence of more natural routes to the treatment of post-stroke depression using acupuncture and musical therapy. The patient in their case report was a 53-year-old male who suddenly developed weakness in the right limbs

one month prior to review. The patient's stroke diagnosis was later complicated by post-stroke depression and a generally pessimistic outlook on life (Lin et al., 2018). According to Lin et al., (2018) "Transcranial Doppler (TCD) showed occlusion of extracranial segment of internal carotid artery (ICA) on [the] left side, opening of exterior branches of ICA on [the] left side, opening of [the] exterior left ramus communicans, severe stenosis of terminal ICA on [the] right side, and severe stenosis of initial middle cerebral artery (MCA) on [the] right side." Lin et al. (2018) treated the patient with acupuncture with specific acupoints selected including:

> "Baihui (GV 20), 3 brain acupoints consisting of Shenting (GV 24) and Benshen (G 13) of both sides, 3 hand acupoints comprising of Quchi (LI 11), 35 Waiguan (SJ 5) and Hegu (LI 4) on right side, Shousanli (LI 10) on right side, and 3 foot acupoints consisting of Zusanli (ST 36), Sanyinjiao (SP 6) and Taichong (LR 3) on right side. The location of acupoints referred to international standards. Baihui was located in the brain, 5 cun from the midpoint of anterior hairline straightly, or the midpoint of the line of 2 ear tips" (Lin et al., 2018).

The musical therapy administered to the patient along with acupuncture is referred to as Traditional Chinese medicine five-element musical therapy. This form of therapy asks the patient what type of music he/she enjoys listening to, and is usually selected based on the patient's emotions, and based on the principles of mutual generation, mutual suppression, and mutual correspondence (Lin et al., 2018). After being treated for post-stroke depression simultaneously with acupuncture and musical therapy, Lin et al. (2018) found that with treatment of the mind and body, "the patient's neurological deficit score, HAMD scale and ADL scale scores were improved significantly, and the levels of TNF-α, IL-6, hs-CRP and homocysteine, biological indicators that were in close association with the pathogenesis of PSD, were reduced

prominently, with satisfactory therapeutic efficacy obtained." Thus, while acupuncture and five-element musical therapy suggest a strong benefit for this case study of a post-stroke depressed patient, one major limitation of the study is the small sample size, limited demographics, and single sex study parameters. Therefore, in order to further establish the benefits of acupuncture and musical therapy for the treatment of cardiovascular and neurological related illnesses, accompanied with depression, further study must be conducted using larger and more diverse populations. Additionally, the case study by Lin et al. (2018) administered the simultaneous treatment of acupuncture and musical therapy. Thus, it becomes difficult to isolate the true influence of each non-pharmacologic therapeutic modality independently.

The predominance of research investigating the link between depression and cardiovascular health delves into how psychological and emotional well-being influence health outcomes in patients with cardiovascular disease, as well as in patients with the absence of heart disease. Researchers DuBois, Lopez, Beale, Healy, Boehm, and Huffman (2015) investigated the correlation between positive psychological constructs (optimistic viewpoints and mentality) on various health-related outcomes in patients with cardiovascular disease. DuBois et al. (2015) completed a systematic review of prospective observational studies using the search engines PubMed and PsycINFO from January 2014 to the time of their proposed research (2015). Inclusion criteria consisted of any article discussing the "effects of a positive psychological construct on subsequent health-related outcomes (including mortality, hospitalizations, self-reported health status) in patients with established heart disease" (DuBois et al., 2015). A total of 30 studies met inclusion criteria. Researchers found that among patients with cardiovascular disease, optimism and a positive psychological state was prospectively associated with cardiac health but additional research must be conducted to confirm these findings.

Patients who have recently experienced cardiac health events are most often treated for depression or anxiety using psychological measures with the intention of improving the general health outcomes. Richards et al. (2017) were interested in discovering the effects "of psychological interventions (alone or with cardiac rehabilitation) compared with usual care (including cardiac rehabilitation where available) for people with CHD on total mortality and cardiac mortality; cardiac morbidity; and participant-reported psychological outcomes of levels of depression, anxiety, and stress; and to explore potential study-level predictors of the effectiveness of psychological interventions in this population." The trial participants were mostly men between the ages of 53 and 67 years. After performing a meta-analysis of 35 studies included 10,703 people with cardiovascular disease, the authors concluded that psychological treatments for people with cardiovascular disease had no impact on total mortality, the risk of revascularization procedures, or on the incidence of myocardial infarction that was non-fatal. However, "cardiac mortality was reduced and psychological symptoms (depression, anxiety, or stress) were alleviated; the GRADE assessments suggest considerable uncertainty surrounding these effects" (Richards et al., 2017). Moreover, according to Wells et al. (2018), there is a lack of psychological intervention for anxiety or depression for patients attending cardiac rehabilitation services. Despite the lack of mental health integration in cardiac rehabilitation settings, anxiety and depression among cardiac patients remains high. Even with the advancements in treatments and therapy for atherosclerosis, cardiovascular disease remains the leading cause of death in the U.S. and worldwide (Levine et al., 2017; NIMH, 2017; WHO, 2018).

A strong, bidirectional and graded relationship exists between depression and cardiovascular disease. In the enhancing recovery in coronary heart disease (ENRICHD) trial,

74% of patients who had recently suffered from a myocardial infarction were also diagnosed with major depression (Dhar & Barton, 2016). While an average of 10% of the general population are diagnosed with major depression, this percentage increases to 40% in people who have suffered a major cardiac event, 30% in people who have cardiovascular disease, and in 50% of those recovering from coronary artery bypass surgery (Dhar & Barton, 2016). Therefore, the alleviation of depression should facilitate the successful alleviation of cardiovascular disease, and vice-versa.

The majority of research investigating the effects of various forms of non-pharmacotherapy for the treatment of depression and cardiovascular disease has shown benefits for patients. Psychotherapy is a form of non-pharmacotherapy which encompasses any intervention where the core element is verbal communication between the depressed subject and the therapist. Psychotherapy has been shown to improve depressive symptoms and quality-of-life domains including social relationships, physical abilities, mental health functioning, and engagement in daily activities—all of which patients with depression experience deficits. Psychotherapy also improves the mental and physical health of patients. Short-term psychotherapy of 8-or-fewer sessions is shown to be as effective in reducing symptoms of depression as standard duration psychotherapy consisting of 12 to 20 sessions. Effect sizes for brief psychotherapy are modest but at present appear comparable to those observed in trials of antidepressant medications and of standard duration psychotherapies. Moreover, for patients with severe depression, 16 sessions of psychotherapy were found to be more effective in reducing symptom severity than only 8 sessions.

A common form of psychotherapy, cognitive behavior therapy, improves symptoms of depression in cardiac patients. Research shows no significant difference in patient outcomes

between cognitive behavior therapy and brief psychotherapy on depression scales: BDI-II, major rates of depression, or the HADS-A score. While no significant difference exists between cognitive behavior therapy and brief psychotherapy for depressed cardiac patients, group psychotherapy sessions reduce symptom severity in these patients. Additionally, short-term cognitive behavior therapy is an effective treatment option for acute unipolar depression, and short-term psychodynamic psychotherapy (PAT) was found equally effective compared to short term CBT and other psychotherapies (Leuzinger-Bohleber et al., 2019).

For patients with pharmacotherapy treatment-resistant depression, cognitive-behavioral therapy is equally effective for depression as antidepressant therapy alone, and combining cognitive-behavioral therapy and antidepressant therapy is even more effective (Nakagawa et al., 2017). Furthermore, psychotherapy has greater positive effects on mental health as compared to physical health. However, despite the smaller effect, physical health is an important predictor of cardiovascular health (Chaddha et al, 2016). Additionally, depressed persons have approximately a two-fold increased risk of having or developing cardiovascular disease. Following a cardiovascular event, the risk of onset of depression is increased, resulting in poorer cardiovascular outcomes. Given the prevalence of comorbid depression and cardiovascular disease, cognitive behavior therapy for depression likely plays a dual role in reducing the risk for cardiovascular disease.

Moreover, a beneficial relationship exists between positive thoughts and physical wellbeing and the practice of meditation is shown to reduce both depression and cardiovascular symptoms in patients (Levine et al., 2017). Eight weeks of mindfulness-based stress reduction meditation reduces perceived stress and anger in cardiac patients, and meditation has been shown to improve overall quality-of-life. Meditation therapy, particularly mindful meditation, has also

been shown to lower blood pressure and the relationship between blood pressure and the increased risk of cardiovascular disease is well-established in the medical community. Furthermore, transcendental meditation is shown to lower blood pressure in African American men and women with angiographically documented coronary artery disease, and decreases carotid artery thickness in cardiac patients (Levine et al., 2017). Researchers Levine et al. (2017) concluded that transcendental meditation has positive effects on atherosclerosis and thus may reduce the risk for cardiovascular disease. Therefore, therapies of the mind undoubtedly have an influence on our physical health, especially when discussing heart health.

Acupuncture is another non-pharmacotherapeutic technique shown to be effective in reducing the symptoms of depression in post-stroke cases. After being treated for post-stroke depression simultaneously with acupuncture and musical therapy, Lin et al. (2018) found that with treatment of the mind and body, neurological deficit scores, HAMD scale and ADL scale scores were improved significantly, and levels of markers for cardiovascular disease including TNF-α, IL-6, hs-CRP and homocysteine, were reduced significantly. Further research is needed investigating the positive effects of acupuncture on comorbid depression and cardiovascular disease.

Lastly, physical exercise is widely known to alleviate the symptoms of depression and reduce the risk of cardiovascular disease in patients and is strongly encouraged by the health care community (Knapen et al., 2014). In patients with mild to moderate depression, exercise is as effective for the reduction of depressive symptoms as antidepressant medication (Knapen et al., 2014). Not only is exercise an effective non-pharmacologic treatment option for patients with major depression, physical exercise also improves physical health (e.g. metabolic syndrome), body image, and patients' coping strategies with stress, quality-of-life, and independence in

activities of daily living in older adults. Thus, physical exercise is encouraged for the management of both depression and cardiovascular disease, as well as in reducing the risk factors associated with both conditions.

Chapter 5

Discussion

Depression and cardiovascular disease are two of the most common and detrimental disease states, with depression being the number one cause of disability and cardiovascular disease being the leading cause of death around the world. While there is undoubtedly a plethora of advantages to conventional medicine using pharmacotherapy for the treatment of acute and chronic disease, there are serious fears and misunderstandings in the general public about pharmaceuticals leading patients to avoid compliance with physician guidance and medical interventions for their illnesses (American Medical Association, 2015). As stated by the American Medical Association (2015), the most common reasons for non-adherence to physician guidance and prescribed medications include: a fear of unwanted and painful side-effects, fear of dependence; and the high cost of medications. In the United States, depression and cardiovascular disease are typically treated using Western medical practices mostly consisting of a prescription medication regimen that reportedly drastically increases the pain and suffering of patients due to adverse side-effects (Lin et al., 2018). Thus, it becomes imperative for the scientific and medical community to discover integrated and/or non-pharmaceutical routes to treating depression and cardiovascular disease, where patients are more likely to engage in positive lifestyle changes—thereby reducing or potentially avoiding the fears associated with pharmacotherapy, unless medication is otherwise indicated.

The majority of research investigating depression and cardiovascular disease shows a strong bidirectional and graded correlation between the two health conditions, which are most-often-than-not comorbid states of illness—the more severe one condition, the more severe the

other. Depression has a strong worsening effect on cardiovascular disease and people with cardiovascular disease have higher rates of depression than the general population. Research suggests that unhealthy lifestyle factors (smoking, diets high in calories, salt, and saturated fats), living a sedentary lifestyle, nonadherence to physician guidance and prescribed medications, type A personality, increased inflammation and oxidative stress, decreased heart rate variability, hyperactivation of the HPA axis, endocrine system dysfunction, omega-3 impairment, excessive stimulation of the sympathetic nervous system, nucleotide polymorphisms, circadian desynchronization and sleep cycle dysfunction, genetics factors, and metabolic syndrome—all contribute to and increase the risk for both depression and cardiovascular disease.

Therefore, health professionals should urge the medical community to incorporate various forms of non-pharmacologic modalities, along with conventional approaches if necessary, for treating depression and cardiovascular disease. Because the strong association between depression and cardiovascular disease has only been more recently studied and recognized by researchers and the medical community, not enough data is available on the health benefits of non-pharmacotherapy as it compares to medicines for the alleviation of comorbid depressive and cardiovascular symptoms. However, the small number of research available on the influence of various non-pharmacology on depression and cardiovascular disease show promising results pointing to a myriad of health benefits for the treatment of depression in cardiac patients with both conventional and non-pharmacologic treatment, used together or independently as appropriate for the individual patient. Research even shows non-pharmacotherapy, including psychotherapy, meditation, and acupuncture to be as effective as antidepressant medication in treating depression (Nieuwsma et al., 2018).

Various forms of psychotherapy including interpersonal therapy, problem-solving therapy, mindfulness-based cognitive therapy, cognitive-behavioral analysis system of psychotherapy, dialectical behavioral therapy, functional analytic psychotherapy, acceptance and commitment therapy, and short-term psychodynamic therapy have all been shown to reduce the symptoms of depression in depressed patients, and heart disease independently of one-another, with or without antidepressant medication (Nieuwsma et al., 2018). Furthermore, non-pharmacotherapy including exercise therapy, meditation, acupuncture, and five-element musical therapy, were all shown to reduce the symptoms of depression and cardiovascular disease in patients and are indicated for the future of integrative medical practice (Levine et al., 2017; Lin et al., 2018).

Finally, steering away from prescription medications when possible to alleviate or treat symptoms of depression and cardiovascular disease by implementing non-pharmaceutical treatment options for patients may be the answer to reducing disease burden in the future by making patients more motivated, inclined, and less fearful of addressing their health problems. However, when medication is necessary and indicated for the patient, an integrated approach to disease management using both conventional and non-pharmacologic therapies may be optimal. Furthermore, while various forms of non-pharmacotherapy are effective in reducing the symptoms of both depression and cardiovascular disease independently, it remains undetermined whether these treatments are effective is reducing comorbid depression and cardiovascular disease.

Analysis of Strengths and Weaknesses

Strengths. This research paper is balanced to show the interrelationship between depression and cardiovascular disease, as well as the benefits of non-pharmacotherapy for the

treatment of both health conditions. Most of the literature analyzed were meta-analytic reviews of randomized controlled trials investigating these relationships, as well as single studies where a randomized controlled trial was carried out to highlight any correlation between depression, cardiovascular disease, and non-pharmacotherapies for treatment.

Weaknesses. The relationship between depression and cardiovascular disease and non-pharmacotherapy for the treatment of depression and cardiovascular disease are well analyzed. However, the paucity of research available investigating the effects of diverse forms of non-pharmacotherapy on comorbid depression and cardiovascular disease hinders the scientific and medical communities' confidence in determining non-pharmacological modalities and conventional medicine as a single or multimodal treatment protocol for both disease conditions. While a graded and bidirectional relationship between depression and cardiovascular disease exists, a lack of attention is paid to the amelioration of these diseases using non-pharmacotherapeutics for comorbid depression and cardiovascular disease.

Proposed Future Study

A graded and bidirectional relationship between depression and cardiovascular disease has been established and "there is no argument that depression is a risk marker for an increased incidence of new cardiovascular disease and a worse outcome in existing cardiovascular disease" (Hare et al., 2013). However, there is a scarcity of research investigating the effects of non-pharmacotherapy on comorbid depression and cardiovascular disease. Therefore, future research exploring the effects of various forms of non-pharmacotherapy on comorbid depression and cardiovascular disease should be conducted to determine which are most beneficial to patients, and whether certain non-pharmacotherapies should be a standard treatment protocol for cardiac

patients with or without formally diagnosed major depressive disorder or clinical depression. When indicated, implementing an integrated, multi-disciplinary approach with both conventional and non-pharmacologic techniques for clinical depression and CVD patient care and management may be a key strategy for managing depression in the context of cardiovascular disease, or vice-versa.

Proposed Study Design: A case series trial should be initiated using specified inclusion and exclusion criteria with a maximum of 20 subjects due to feasibility.

Participants: A total of 20 patients 18-years-or-older will be gathered from the Middlesex Hospital Family Medicine Center, located in Middletown, Connecticut. Participants will be required to sign informed consent that they are voluntarily foregoing pharmaceutical interventions for the management of either depression and/or cardiovascular disease and understand the potential health consequences. Patients will be required to have a formal diagnosis and/or history of both cardiovascular disease and major depressive disorder (clinical depression). Any form of cardiovascular disease including a history of myocardial infarction, coronary atherosclerosis, stroke, heart failure, angina, hypertension, arrythmia, atherosclerotic calcification, and/or heart valve problems, will be included. A formal diagnosis of major depressive disorder or clinical depression will follow the criteria set form by the DSM-V. As outlined in the DSM-V, to be diagnosed with major depressive disorder, patients must have at least five of the following symptoms of depression for at least a two-week period diagnosed by a licensed medical or mental health professional (at least one symptom must be a reduced interest or pleasure or depressed mood): depressed mood (for children and adolescents, this can also be an irritable mood); diminished interest or loss of pleasure in almost all activities (anhedonia); significant weight change or appetite disturbance (for children, this can be failure to achieve

expected weight gain); sleep disturbance (insomnia or hypersomnia); psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness; diminished ability to think or concentrate; indecisiveness; recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide (Medscape, 2019).

The Middlesex Hospital Family Medicine Center provides patients with an Integrative Medicine Consultation Program offering acupuncture, yoga, nutrition planning, exercise, spinal manipulation, relaxation therapies, massage, mental health counseling, as well as medication and other conventional therapies. Subjects will be randomly divided into four separate groups to either receive non-pharmacotherapy with mental health counseling using cognitive behavior therapy, acupuncture, meditation therapy, or all three treatments. Subjects will be recruited through their primary care physicians within the Middlesex Hospital patient database. Advertisements will also be placed in the various medical inpatient and outpatient offices affiliated with Middlesex Hospital in Middletown, CT, and surrounding areas. Patient outreach will also consist of an emailed newsletter, social media ads, and placing fliers in the area locally. All services will be provided gratis to all participants.

Inclusion Criteria: The following inclusion criteria should be considered: adults 18-years-or-older; male and female subjects; subjects formally diagnosed with any form of cardiovascular disease including a history of myocardial infarction, coronary atherosclerosis, stroke, heart failure, angina, hypertension, arrhythmia, atherosclerotic calcification, and/or heart valve problems. Those diagnosed with major depressive disorder following criteria set forth by the DSM-V; subjects must be diagnosed or have a history of both cardiovascular disease and clinical depression.

Exclusion criteria: Diagnosis with any form of mental illness other than major depressive disorder. Any other comorbidity other than depression and/or cardiovascular disease. Those already receiving psychotherapy; those taking antidepressant medication; or those engaging in cardiac rehabilitation or taking any medication for cardiac health including statins, beta-blockers, or ace-inhibitors. Those partaking in any severely restricted diets or exercise programs for CVD currently.

Methods: Subjects will be randomized to receive treatment in either one-of-four groups: cognitive behavior therapy, meditation, acupuncture, or all three treatments, the study will run for 16-consecutive weeks.

Cognitive behavior group: Participants will receive psychotherapy by a licensed psychotherapist once-per-week for one hour for a 16-week period. Psychotherapists treat mental disorders with psychological rather than medical means (Mayo Clinic, 2016). Cognitive behavior therapy is one form of psychotherapy in which the psychotherapist helps the patient identify unhealthy, negative beliefs and behaviors and replace them with healthy, positive ones (Mayo Clinic, 2016).

Meditation group: Participants will receive group stress-reducing techniques and meditation therapy by a licensed meditation practitioner once-per-week for 16-weeks. Meditation can produce a state of deep relation for the patient, and is often practiced to reduce stress and anxiety. The practice of meditation involves a focused attention on a conscious elimination of negative and "jumbled" thoughts that may be causing stress. Meditation is recognized for producing an enhanced emotional and physical wellbeing through relaxed breathing, focused attention, a quiet setting, and a comfortable position (Mayo Clinic, 2017).

Acupuncture group: Participants will receive one-hour of Traditional Chinese Medicine Acupuncture by licensed or certified acupuncturists who will be instructed to use the same meridian points for targeting depression and cardiovascular disease—for all patients. Patients will receive one-hour of acupuncture each week for 16-weeks. Subjects in the all-three treatments group will receive all three treatments (cognitive behavior therapy, meditation therapy, and acupuncture) for 16-weeks at the same rate and times as subjects in the other three experimental groups.

Information on sex, age, weight, body mass index (BMI) and education level will be gathered at the initiation of the study. BMI for all participants will be obtained using a bioimpedance scale which is used to measure the percentage of body fat in relation to lean body mass. A comprehensive lipid panel to assess cardiovascular health will be performed for all patients at baseline and following 16-weeks of non-pharmacologic treatments. Biomarkers of cardiovascular disease should include total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, homocysteine, apolipoprotein B, lipoprotein A (lipoprotein subfractions), C-reactive protein, insulin, HbA1C, and fasting glucose. Information from subjects on chest pain frequency, chest pain duration (minutes), and chest pain severity on a scale of 1-10, will also be gathered at baseline and at 16-weeks. Blood pressure readings will be performed for all participants at baseline and after 16-weeks. Non-pharmacologic therapies should be provided once-per-week for a 1-hour period by licensed health care professionals instructed on a standard treatment protocol for all subjects.

Testing for mental health will be administered at baseline and following 16-weeks of non-pharmacotherapy for all four groups. Scores from the Patient Health Questionnaire-9 (PHQ-9), Beck Depression Inventory (BDI), and the Hamilton Rating Scale for Depression (HRSD)

will be gathered and analyzed for any changes in mental health in subjects. The Cardiac Depression Scale will also be administered to measure depression in cardiac patients and will be provided at baseline and following 16-weeks of non-pharmacotherapy to assess any changes or improvements in depressive symptoms among participants in all four groups. Urinary neurotransmitter testing (UNT) for serotonin and dopamine using monoamine assays will be administered at baseline and after 16-weeks of treatment (Hinz, Stein, Trachte, & Uncini, 2010). Results of UNT for serotonin and dopamine will be compared for changes or improvements, and whether they correlate to improvements in self-reported depression severity in the PHQ-9, BDI, and HRSD following 16-weeks of therapy. A comprehensive fatty acids test will also be administered to patients at baseline and following 16-weeeks of therapy. The comprehensive fatty acids test provides levels of over 30 markers and total levels of saturated, monounsaturated, polyunsaturated, omega-3, omega-6, eicosapentaenoic acid, docosahexaenoic acid, gamma-linolenic acid and other fatty acids using 2 mL of collected serum following a 24-hour fasting period where no alcohol is consumed (The Great Plains Laboratory, Inc., n.d.). Lipid panel levels and depression scale scores will be administered and analyzed for all subjects at baseline and at the completion of 16-weeks of therapy for all groups.

At the conclusion of the study, results of non-pharmacotherapy treatment on patients with comorbid depression and cardiovascular disease will be assessed to determine the extent of the effects of cognitive behavior therapy, meditation, and acupuncture, or all three therapies, on depression and cardiovascular disease in patients. Close analysis of any changes in scores on the Health Questionnaire-9 (PHQ-9), Beck Depression Inventory (BDI), the Hamilton Rating Scale for Depression (HRSD), and the Cardiac Depression Scale at baseline and at the completion of the study should help determine the effects of cognitive behavior therapy, meditation, and

acupuncture on depression. Meanwhile, lipid panel levels for total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, homocysteine, apolipoprotein B, lipoprotein A (lipoprotein subfractions), C-reactive protein, insulin, HbA1C, fasting glucose, and comprehensive fatty acids will be assessed for cardiovascular health status. Any changes in chest pain frequency, chest pain duration (minutes), and chest pain severity on a self-reported scale of 1-10 should help determine whether cognitive behavior therapy, meditation, and acupuncture, or all three therapies combined, have a positive influence on cardiovascular health. Subjects with comorbid depression and cardiovascular disease should be analyzed for any improvements with non-pharmacologic therapies by assessing all scores on tests for both depression and cardiovascular disease.

Conclusions: the proposed future study might help to determine the effects of non-pharmacotherapy, including psychotherapy, meditation, acupuncture, or all three therapies, and their influence on comorbid major depressive disorder and cardiovascular disease. If results of the study indicate positive effects of these forms of non-pharmacologic therapy on comorbid depression and cardiovascular disease, a multimodal and integrative approach to treating depression and cardiovascular disease may be the key for the proper diagnosis, management, and treatment of these leading health disparities. Since depression and cardiovascular disease have a graded and bidirectional relationship, the successful alleviation of one condition should lead to the successful alleviation of the other.

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