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The Role of Inflammatory Biological Markers in Novel Pharmacotherapies For Populations with Depression

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Abstract

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For Populations with Depression

by

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MA, Brown University, 2009

BS, University of Rhode Island, 2004

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Abstract

Current interventional pharmaceutical therapies targeted for depression are not adequate to achieve sufficient remission following treatment. Researchers explored inflammatory biomarkers as a way of understanding why treatment for depression is effective for some and not others. The purpose of this secondary data analysis study was to determine if there was a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission. Using the immune-cytokine paradigm of depression (POD) allowed depression to be viewed as multifaceted and a potential signal of chronic immune system activation. This secondary data analysis included findings from a clinical trial called, "A Study of the Efficacy and Safety of CP-601,927 Augmentation of Antidepressant Therapy in Major Depression." ANOVA and linear regression were used to analyze 1 dependent variable: depression remission. The 5 independent variables included adiponectin C-Reactive Protein (hs-CRP), leptin, interleukin 1-β (IL1-β), interleukin 6 (IL6), and tumor necrosis factor-α (TNFα). The 3 mediating variables included age, race, and gender. According to the results of the study, IL6 significantly correlated with and predicted remission outcome, as measured by change in MADRS total score from baseline. None of the other biomarkers significantly correlated with remission outcome. Better remission outcomes for patients suffering from depression would lead to positive social change and improved quality of life.

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Dedication

This dissertation is dedicated to my loving and supporting partner in life, Paula, and our exuberant, kind-hearted boys, Bennett and Landon.

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Chapter 1: Introduction to the Study

Introduction

In the United States, depression is one of the most common mental disorders affecting adults. In 2014, 6.7% of all U.S. adults had at least one major depressive episode (National Institute of Mental Health [NIMH], 2016b). Despite the prevalence of this condition, treatment options continue to vary in efficacy (Fava & Rush, 2006; Lopresti, Maker, Hood, & Drummond, 2014; Strawbridge et al., 2015). Researchers looked to inflammatory biomarkers as a way of understanding why treatment for depression was effective for some and not others (Krishnadas & Cavanagh, 2012; Roy & Campbell, 2013). In this study, the influence of inflammatory biomarkers on treatment efficacy and remission was examined. Data relating to the influence of inflammatory biomarkers and depression treatment efficacy has the potential to inform which pharmacotherapies should yield the greatest benefit to which subpopulation suffering from depression (Hashimoto, 2015; Strawbridge et al., 2015). Research in this area could lead to better remission outcomes for patients suffering from depression as a direct result of doctors' abilities to tailor treatments to their patients.

For this chapter, several topics are discussed to further expound on the research topic. The organization of the chapter is comprised of the following: (a) background of the study, (b) problem statement, (c) purpose of the study, (d) research questions and hypotheses, (e) conceptual framework, (f) nature of the study, (g) definitions, (h) assumptions, (i) scope and delimitations, (j) limitations, and (k) significance of the study.

The chapter ends with a summary of the chapter and an overview of the contents of the rest of the dissertation.

Background

Depression, even in severe cases, is considered a treatable condition (NIMH, 2016a). However, people are affected differently by depression, and treatment can often take a trial and error approach, using medications, psychotherapy, or electroconvulsive therapy (NIMH, 2016a). Depression is considered a highly heterogeneous disease, for which alternative approaches to investigating new therapies should be considered (Kennedy & Risvi, 2009).

Treatment

Options for treatment of depression include antidepressants, exercise, alternative medicine, and psychological interventions. These treatment options can even be combined. However, many patients are treated for depression by primary care physicians and are likely to receive a prescription for an antidepressant. Antidepressants work by selectively targeting neurotransmitters, such as serotonin reuptake inhibitors, serotonin, and norepinephrine reuptake inhibitors (Gartlehner et al., 2016; Steidtmann et al., 2013). These medications usually take between 2 and 4 weeks to become effective and are taken for a duration of 6 to 12 months (NIMH, 2016a).

Remission

The largest clinical trial ever conducted in depression, STAR*D, showed that remission rates in the study clinics were lower than expected, suggesting the need to establish several steps to achieve remission for most patients (Gaynes et al., 2009). Both

switching and augmenting antidepressant therapies appeared reasonable options when an initial antidepressant treatment failed; however, these two strategies could not be directly compared (Gaynes et al., 2009; Strawbridge et al., 2015). There is an unmet need to develop novel approaches to therapeutic strategies for interventions targeted for populations diagnosed and suffering from depression to enhance treatment outcomes in depression (Fava & Rush, 2006; Lopresti et al., 2014; Strawbridge et al., 2015).

Although there was a correlation between biomarkers and depression, inflammatory biomarkers might play a role in the pathophysiology of depression, warranting investment in further investigation (Krishnadas & Cavanagh, 2012; Roy & Campbell, 2013). Increased concentrations of inflammatory biomarkers might predict a lack of response to therapeutic interventions, which might circumvent the mechanisms of action of conventional antidepressants (Raison et al., 2013). Dysregulation of the immune system and increased activation of the inflammatory response system that accompanies depression may provide predicative response cues to the level of efficacy response (Dowlatia et al., 2010). The symptoms of depression and activation of an inflammatory response have the potential to alter the remission outcome following intervention with standard therapies targeted for depression (Miller, Freedland, Carney, Stetler, & Banks, 2003). Characterization of and profiling of inflammatory biomarkers may also present an opportunity to identify populations diagnosed with depression for other high risk diseases (e.g., cardiovascular diseases; Zeugmann, Quante, Heuser, Schwarzer, & Anghelescu, 2010). Essentially, although inflammatory biomarkers play a role in the etiology of

depression, these may also contribute to therapeutic response (Maes, Mihaylova, Kubera, & Ringel, 2012).

Problem Statement

Current interventional pharmaceutical therapies targeted for depression are not considered adequate enough to achieve sufficient remission following treatment (Hashimoto, 2015; Slavich & Irwin, 2014; Wray et al., 2012). Depression yields a burden regarding adverse symptomatology, decreased productivity, and increases in morbidity (Wray et al., 2012). Moreover, depression contributes to the facilitation of rising mortality as a result of suicide (Wray et al., 2012). In clinical trial data examining outcomes in depression, scholars have historically demonstrated that achievement of remission is decreasing (Gartlehner et al., 2016; Gaynes et al., 2009; Steidtmann et al., 2013). Such data indicate that a need to implement strategies that adequately stratify subpopulations to determine among which groups remission rates are decreasing and to examine how remission outcomes can be successfully met for these groups (Gaynes et al., 2009; Lopresti et al., 2014). The problem researched by this study was the relationship between inflammatory biomarkers and treatment efficacy for depression. These inflammatory biomarkers respond to the psychosocial stressors associated with depression, and these both precede and follow diagnosis with major depressive disorder (Miller & Raison, 2016).

Inflammatory biomarkers, such as adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα affect the effectiveness of newly developed antidepressants. Research efforts investigating the role biomarkers played in depression also have the potential to inform

which pharmacotherapies should yield the greatest benefit to the subpopulation suffering from depression (Hashimoto, 2015; Strawbridge et al., 2015).

Drug development researchers have not examined the role of biomarkers in identifying populations affected with depression for inclusion in clinical trials (Gaynes et al., 2009). This study might add insight into the relationship between biomarkers and treatment efficacy, thereby improving treatment options and outcomes. The role of inflammatory biomarkers in the etiology of depression was characterized; however, how this translated to therapeutic outcomes remained unclear (Strawbridge et al., 2015). The Montgomery Åsberg Depression Rating Scale (MADRS) total score was used to measure efficacy. The results of this research might help clinicians and scientists to increase remission rates by increasing understanding of the role inflammatory biomarkers played in whether the drug worked, potentially fostering achievement of remission.

Purpose of the Study

The purpose of this secondary data analysis study was to determine if there was a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission. I analyzed an existing dataset from a sponsored experimental, randomized, double-blind, placebo-controlled, and institutional review board (IRB)-approved clinical trial with the purpose of identifying relationships between the inflammatory biomarkers and depression treatment efficacy, depression remission outcomes, and depression treatment response. These data were analyzed using a multiple linear regression analysis, while controlling for the demographic variables of age, race, or gender in persons diagnosed with

depression. The theory guiding this research was the immune-cytokine paradigm of depression (POD; Smith, 1997), as it provided a framework for understanding how depression was a multifaceted condition and a signal of chronic immune system activation (Smith, 1997).

Research Questions and Hypotheses

Based on the immune-cytokine POD and lack of research on inflammatory biomarkers in mental health, the following included research questions and associated hypothesis:

RQ1: Is there any relationship between inflammatory biomarkers, including adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H1_o$: There is no relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H1_a$: There is a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

RQ2: Is there any relationship between remission outcomes, as measured by MADRS uniform for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H2_o$: There are no relationships between uniform remission outcomes for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H2_a$: There is a relationship between uniform remission outcomes for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

RQ3: Is there any relationship between treatment response, as measured by the MADRS, and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H3_o$: There is no relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H3_a$: There is a relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

Theoretical Framework for the Study

The immune-cytokine POD (Smith, 1997) was used to support the research on inflammatory biomarkers and depression treatment efficacy. This framework provides a mechanism to search new areas for causes of depression (Roy & Campbell, 2013; Smith, 1997). There are four central tenets of this paradigm:

1. There is two-way communication between the brain and the immune system, whereby the immune system can affect the brain (via excretion of cytokines) and the brain can affect immune system function.
2. The immune system has two-way communication with the endocrine system, which is important because endocrine activation is common in depression.
3. Physical stressors (infection, trauma, cancer, organ dysfunction, etc.) activate the immune system and the secretion of cytokines by the brain.
4. Mental stressors have the same affects as physical stressors. This framework is useful for this study because depression could be thought of as multifaceted and a signal of chronic immune system activation. (Smith, 1997)

Understanding the role of inflammatory biomarkers regarding treatment through the immune-cytokine POD lens potentially revealed other factors in chronic depression and their correlating treatments.

Nature of the Study

This research study was a quantitative secondary data analysis from an existing dataset from a sponsored experimental, randomized, double-blind, placebo-controlled, and IRB-approved clinical trial (ClinicalTrials.gov Identifier: NCT01098240). I focused on the comparison of an add-on novel pharmacotherapy and placebo in a population diagnosed with depression who demonstrated a previous lack of remission.

This secondary data were used to determine if any correlational relationship existed between the variables of inflammatory biomarkers and treatment efficacy. The quantitative design was useful for addressing the research questions because I assumed a narrow-angle lens that focused on testable hypotheses. Executing a post hoc, secondary data analysis on a randomized controlled trial design assisted me in determining how the intervention (i.e., the novel pharmacotherapy) influenced the observed outcome (i.e., the level of efficacy achieved) in those diagnosed with depression (West & Spring, 2010). Employing a randomization process statistically specified the number of participants to inform allocation to either the intervention (i.e., the novel pharmacotherapy) or control (i.e., placebo) group. This approach minimized the systemic differences between these groups, as these related to both observed and unobserved variables, ensuring internal validity remained conserved (West & Spring, 2010).

Definitions

Depression: Depression is a mood disorder that affects how a person thinks and feels, as well as his or her ability to complete daily activities such as eating, sleeping, or working. The symptoms of depression must be persistent for 2 weeks or more to result in a diagnosis of depression. Forms of depression include persistent depressive disorder, perinatal depression, psychotic depression, seasonal affective disorder, disruptive mood dysregulation disorder, and premenstrual dysphoric disorder (NIMH, 2016a).

Inflammatory biomarkers: Acute and chronic inflammatory responses in the body are largely the result of cytokines (Brenner et al., 2014). Cytokines are small proteins that are secreted from cells that can serve as proinflammatory or antiinflammatory agents.

The term cytokines is a general name for these proteins; examples of cytokines include adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα (Zhang & An, 2007). Cytokines are believed to be at the core of depression due to the influence on neuropsychiatric symptoms and interrelatedness with the immune system, brain, and endocrine system (Smith, 1997).

Remission: Remission, regarding depression, is traditionally defined phenomenologically. It is generally defined based on a score on a standardized scale, such as the Hamilton Rating Scale for Depression; however, patients' return to their usual self and usual level of functioning can also be considered (Zimmerman et al., 2014).

Assumptions

To conduct this study, I made several assumptions. These assumptions related to the validity of the secondary data included in the study, the study of the biomarkers identified in this study, and the use of the identified conceptual framework. Additionally, it was assumed that the original study was conducted based upon ethical standards and principals for the conduct of clinical research. Given the context of the study, these assumptions were necessary and critical to the study.

Validity of Data

The data used in this study were collected by Pfizer, Inc. during a clinical study, which was conducted at 25 research centers in the United States between June 2010 and September 2011. Because I used secondary data and not primary data collected by the researcher, I assumed that the researchers who originally collected these data took measures to ensure the validity of the data. This validity included the accurate

measurement of the identified biomarkers, as well as the accurate measurement of depression remission using the MADRS.

Conceptual Framework

The conceptual framework selected for this study was the immune-cytokine POD (Smith, 1997). According to this framework, cytokines play an active role in the presence and subsequent remission of depression due to the influence on the brain, the immune system, and the endocrine system and reaction to physical stressors. Because this was a relatively new perspective from which to view the development and treatment of depression, there was a need for additional research in this area to support its validity in both identification and measurement (Brenner et al., 2014). Therefore, I assumed that this conceptual framework was an appropriate lens through which to view and conduct this study.

Inflammatory Biomarkers

Cytokines is a generic term for the variety of inflammatory biomarkers that are present in the body. There are many of these biomarkers, and these play a variety of roles in the process of inflammation (Brenner et al., 2014). I assumed that the biomarkers, measured in the data included in this study, were appropriate biomarkers to include in the discussion of depression and its treatment. I also assumed that the results from the study involving these specific biomarkers were sufficient for the purpose of applying the results and findings to the research on depression and inflammatory biomarkers as a whole.

Scope and Delimitations

This research study was a quantitative secondary data analysis from an existing dataset from a sponsored experimental, randomized, double-blind, placebo-controlled, and IRB-approved clinical trial (ClinicalTrials.gov Identifier: NCT01098240). I focused on the comparison of an add-on novel pharmacotherapy and placebo in a population diagnosed with depression who demonstrated a previous lack of remission.

The scope of this research study remained limited to the data included in the described data set from a clinical study conducted by Pfizer, Inc. between June 2010 and September 2011. Study participants consisted of outpatients between the ages of 18 and 65 years. The research study remained delimited to the examination of the correlations of the biomarkers; adiponectin; hs-CRP; leptin; IL1-β, IL6; TNFα; depression treatment efficacy; depression remission; and the demographic factors of age, race, and gender.

Other theoretical and conceptual frameworks considered for this study included the affective response model (Zhang & An, 2013) and the social signal transduction theory of depression (Slavich & Irwin, 2014). The affective response model relates to the emotional aspects of depression, not the biological processes that occur with this disorder. The social signal transduction theory of depression involved the biological responses to major life stressors, which I could not measure using the data included in this study. Consequently, the immune-cytokine POD (Smith, 1997) was the most applicable conceptual framework for this study, especially given the study's purpose, research questions, and data. Results of this study would potentially be generalizable, as

these related to the demographic of adults aged 18 to 65 and specifically relating to the biomarkers outlined in this study.

Limitations

This study remained limited as it related to data, the scope of the research, and the chosen research design. The data, selected for this study, were secondary data; therefore, the data were limited to the variables that were already included in this study. Another set of data would need to be collected to examine other variables related to inflammatory biomarkers and depression treatment and remission. Similarly, the scope of the research was limited by the chosen data set. Even though there were many inflammatory biomarkers, the study was limited by the inflammatory biomarkers that were already included in this study. If other biomarkers were to be examined, a new data set would have to be acquired and examined. Finally, the research design was correlational using a multiple linear regression analysis. Consequently, correlation did not imply causation; therefore, this study was limited to examining the relationships between variables rather than identifying causation.

Significance of the Study

Depression is a public health concern for the United States and for the entire world (Johansson, Lundh, & Bjärehed, 2015). Even though standard treatments for depression can be effective, almost two-thirds of patients suffering from major depressive disorder do not respond to treatment using pharmaceuticals (Hashimoto, 2015). This study was significant because it advanced theory, advanced practice, and could lead to positive social change as it relates to understanding and treating depression.

Significance to Theory

The theoretical foundation chosen for this study was the immune-cytokine model of depression (MOD). This theory is a relatively new way of understanding how physical and mental disorders are related (Smith, 1997). This study was significant to supporting immune-cytokine MOD, as well as paving the way for extensions of this theory in the future. In this study, I sought to identify relationships between cytokines (i.e., inflammatory biomarkers) and treatment outcomes for depression. Any results from this study relating to the correlations between these biomarkers and treatment outcomes could help to defend or refute the immune-cytokine theory and help to narrow down the biomarkers more closely related to treatment outcomes compared to others. Additionally, these results could help to narrow the research gap so that future researchers could begin to identify the extent of identified relationships, hypothesize causation, and develop maps of the sequencing of chain reactions between the physical and mental processes that result in the development or remission of depressive disorders.

Significance to Practice

Researchers have described treatment outcomes for depression as "modest" at best (Steidtmann et al., 2013, p. 784). Doctors have used a combination of pharmacotherapy, psychotherapy, and other strategies to achieve the best results for patients, but these treatments are often the result of trial and error. This study was significant to practice because information relating to inflammatory biomarkers and treatment outcomes could assist in prescribing the right treatment for patients the first time. Data, such as from this study, could help doctors to tailor treatments to patients

based on the inflammatory biomarkers that have been presented. This type of treatment could save practitioners time and help to increase their patient success rates and satisfaction.

Significance to Social Change

Researchers have described depression as a "public health burden" (Abel, Hayes, Henley, & Kyyken, 2016, p. 726). Depression costs the United States billions of dollars annually (Greenberg, Stiglin, Finkelstein, & Berndt, 1993). In addition, persons suffering from depression are more likely to commit suicide. Information and data that can assist in more effectively treating depression can lead to positive social change. This study was significant because it could help to narrow the gap in understanding how physical conditions were related to mental conditions as these conditions relate to depression. This information could lead to development of early identification of depressive symptoms, more effective treatment of depression, and the prevention of depression. This could ultimately lead to reduce rates of suicide and reduced medical spending for families and the United States as a whole.

Summary

Depression is of concern in the United States and worldwide. Despite many treatment strategies for depression, there are low rates of continued remission for patients. The emergence of research relating to inflammatory biomarkers is promising in that it can fill in the gaps between understanding how human physical and mental process are related. The purpose of this secondary data analysis study was to determine if there was a relationship between inflammatory biomarkers and treatment efficacy in persons

diagnosed with depression who have demonstrated a previous lack of remission. This chapter has provided information relating to the background of this study, the study problem, and the significance of this study. Chapter 2 contains a review of current and seminal literature relating to the study problem.

Chapter 2: Literature Review

The problem researched by this study was the relationship between inflammatory biomarkers and treatment efficacy for depression. These inflammatory biomarkers respond to the psychosocial stressors associated with depression, and these both precede and follow diagnosis with major depressive disorder (Miller & Raison, 2016). In clinical trial data examining outcomes in depression, scholars have historically demonstrated that achievement of remission is decreasing (Gaynes et al., 2009). There is a need to implement strategies that adequately stratify subpopulations to determine among which groups remission rates are decreasing and to examine how remission outcomes can be successfully met for these groups (Gaynes et al., 2009; Lopresti et al., 2014).

The role of inflammatory biomarkers in the etiology of depression have been characterized; however, how this translated to therapeutic outcomes remained unclear (Strawbridge et al., 2015). The results of this research might help clinicians and scientists to increase remission rates by increasing understanding of the that role inflammatory biomarkers played in whether the drug worked, potentially fostering achievement of remission (Strawbridge et al., 2015). The results of this study provided information on the treatment of depression and the predictors thereof.

The purpose of this quantitative, secondary analysis study was to determine whether there was an association between inflammatory biomarkers and treatment efficacy. I also examined if remission outcomes were uniform for each inflammatory biomarker and attempted to determine whether there was an association between treatment response and inflammatory biomarkers mediated through age, race, or gender.

Literature Search Strategy

The databases accessed to locate the needed literature and published research for this chapter included Google Scholar, DeepDyve, and ERIC. Search terms included *the immune-cytokine model of depression, inflammatory biomarkers, treatment efficacy, depression, inflammatory biomarkers in depression, remission, treatment, age, gender, race, biomarkers, MDD, definition of depression*, and combinations of these terms. To obtain the most current research, sources were prioritized to show literature published within the last 4 years.

Studies believed relevant were included in this chapter. Of the 75 sources obtained for this chapter, 64 articles (85.3%) were published between 2012 and 2016, and 11 articles (14.7%) were published prior to 2012. Types of literature included peer-reviewed articles, clinical trials, and previous studies. All sources were published in peer-reviewed journals. Few concrete studies and articles are available on the effects of inflammatory biomarkers on the treatment efficacy and remission outcomes of patients diagnosed with depression. Therefore, I provided discussion of other studies regarding different treatments of depression, remission outcomes, as well as other theories on depression.

Theoretical Foundation

Depression has been a topic of discussion for decades because so many contradicting views on its cause and effects exist. The theoretical foundation chosen for this study was the immune-cytokine MOD, a new theoretical concept, as a means to understand depression. The immune-cytokine MOD bridged the gap between physical

and mental disorders. According to the immune-cytokine MOD, depression is a chronic physical-biological disorder with mental-emotional symptoms (Smith, 1997).

The immune-cytokine MOD was used to support the research on inflammatory biomarkers and depression treatment efficacy. This framework provided a mechanism to search new areas for causes of depression (Roy & Campbell, 2013; Smith, 1997). There are four central tenets of this paradigm. First, there is two-way communication between the brain and the immune system, whereby the immune system can affect the brain (via excretion of cytokines), and the brain can affect immune system function (Smith, 1997). Second, the immune system has two-way communication with the endocrine system, which is important because endocrine activation is common in depression. Third, physical stressors (e.g., infection, trauma, cancer, organ dysfunction, etc.) activate the immune system and the secretion of cytokines by the brain. Finally, mental stressors have the same effects as physical stressors (Smith, 1997).

From an immunological perspective, cytokines are the core of depression because they cause a plethora of neuropsychiatric symptoms (Smith, 1997). During the 1980s, researchers proved the acute consequences of cytokines on the mood, thought, and behavior of human volunteers. Molecules that are produced by the human body, when taken by humans, results in the symptoms of a depression diagnosis (Smith, 1997). The research was of significance, although psychologists and psychiatrists were not interested in discoveries coming from other fields, such as immunology (Smith, 1997). The immune-cytokine MOD provided a two-way system since 1982. The immune system, via

the secretion of cytokines, can affect brain function (Smith, 1997). There are several different substances known as cytokines. These cytokines are discussed individually.

Interferon-Alpha (INFα)

When monocytes and macrophages are activated, it releases the interferon-alpha (INFα) cytokine. This cytokine provides many benefits for various immune cells, although still carrying various hampering neuropsychiatric effects. Priestman (1980) reported on the effects of interferon-alpha in 1980, and Rohatiner et al. followed in 1983.

Rohatiner et al. (1983) studied 11 human subjects. After giving the volunteers Interferon-alpha intravenously for 7 days, all volunteers felt feverish and fatigued, and they lacked appetite. They also slept a lot, appeared antisocial, were slow to answer questions, and lacked interest in their surroundings (Rohatiner et al., 1983). The abnormal brain waves of the volunteers were similar to those of patients with a brain degenerative disease (Rohatiner et al., 1983). These volunteers could be diagnosed with a major depressive episode after only 1 week. Adams, Quesada, and Gutterman (1984) also studied the effects of interferon-alpha over 4 weeks. As with the abovementioned study, the volunteers also exhibited symptoms of severe depression, although a depressed mood was not present (Adams et al., 1984). It proved that interferon-alpha provokes the symptoms of depression, as well as fits in with the diagnostic paradox (Smith, 1997).

Tumor Necrosis Factor (TNF)

Monocytes, macrophages, and lymphocytes secrete TNF. The properties of TNF are similar to interleukin1, as it can regulate several organs including the brain. The symptoms of TNF on human volunteers, when given intravenously, include fatigue,

anorexia, headaches, muscle ache, and discomfort (Smith, 1997). The symptoms are similar to those of major depression. Headaches are a symptom of many cytokines, but it appears more significant to TNF (Smith, 1997).

Interleukin1 (IL1)

Monocytes and macrophages secrete IL1, and its effects have only been tested on animal subjects. During trials, the animals exhibited symptoms, such as anorexia, reduced activity, loss of interest in usual activities, discomfort, increased sleep, lack of body care activities, reduced social exploration, and less food-motivated behavior (Smith, 1997). These symptoms mimic the symptoms familiar with depression in humans. In another study, Smith (1997) found that stressful social situations, in combination with IL1, caused irritable and hostile behavior of monkeys. This type of behavior also associated with depression (Smith, 1997).

Interleukin-2 (IL2) and Interferon-Gamma (INFγ)

T-lymphocytes secrete INFγ and IL2; low doses of IL-2 produce symptoms of depression, including lethargy, impaired memory, slowed responses, impaired attention, anorexia, lack of interest, and irritability. High doses of IL2 result in hallucinations, delusions, and disorientation, which are associated with schizophrenia. INFγ results in symptoms of fatigue, discomfort, headaches, lack of appetite, weight loss, weakness, lethargy, and decreased concentration, all of which are associated with depression in humans (Smith, 1997).

The abovementioned cytokines have the ability to result in symptoms of depression for most subjects but not all. Cytokines, such as INFα, INFγ, TNF, and IL2,

did not result in depression for all subjects. Taking into account that cytokines are present in every human body and can be produced at any given time provided the right simulation, it is fortunate that the secretion of cytokines do not result in depression 100% of the time. If that was the case, depression rates would be much higher (Smith, 1997). Furthermore, the experiments only administered one cytokine at a time, which is inconsistent with natural immune activation (Smith, 1997). Naturally, many cytokines are produced at the same time, resulting in a much higher risk of depression (Smith, 1997).

This framework was useful for this study because depression is multifaceted and a signal of chronic immune system activation (Smith, 1997). Understanding the role of inflammatory biomarkers regarding treatment through the immune-cytokine POD lens may reveal other factors in chronic depression and their correlating treatments. Depression is not only multifaceted, but there are also a plethora of variables that influence treatment administration, as well as treatment outcomes. As inflammatory biomarkers have been added to the list of variables for depression, a more recent theoretical framework was needed for optimum analysis.

Literature Review Related to Key Variables and/or Concepts

The number of antidepressants and therapies for depression, which are currently available, is vast; yet, these do not guarantee remission. Current interventional pharmaceutical therapies targeted for depression are not considered adequate enough to achieve sufficient remission following treatment (Hashimoto, 2015; Slavich & Irwin, 2014; Wray et al., 2012). Depression yields adverse symptomatology, decreased

productivity, and increased in morbidity, as well as contributing to rising mortality resulting from suicide (Wray et al., 2012).

In clinical trial data on outcomes of depression, scholars have demonstrated that achievement of remission is decreasing (Gaynes et al., 2009). Cuijpers et al. (2014) posited that there was a correlation between depression and an elevated risk of death for patients; although, it was not clear if the cause of this phenomenon was specific to the disease, patient groups, or a generic result of mortality in certain communities. There is a need for strategies that adequately stratify subpopulations to determine among which groups remission rates are decreasing and to examine how remission outcomes can be successfully met for these groups (Gaynes et al., 2009; Lopresti et al., 2014).

Marrie et al. (2016) have found a correlation between illnesses with an inflammatory component and depression, which resulted in scholars investigating depression alongside inflammatory biomarkers. One of these illnesses is inflammatory bowel disease. Marrie et al. (2016) stated that a correlation existed between depression and anxiety and inflammatory bowel disease (IBD). Furthermore, Marrie et al. mentioned that methods aiding population-based studies on depression and anxiety were needed. Sipido et al. (2016) concluded that depression and anxiety was significantly related to increased levels of C-reactive proteins, as well as high cholesterol. Sipido et al. posited that the results of their study were of significance, as these aided in the explanation of pathophysiological mechanisms connecting depression and anxiety to cardiovascular disease. More information on these pathophysiological links could assist physicians in providing more specialized and individualized treatment for patients (Sipido et al., 2016).

Few researchers have explored the effect of inflammatory biomarkers in adolescence, even though the effect of inflammatory biomarkers was believed to happen at key stages in a patient's life, such as adolescence (Walker et al., 2014). Scholars showed that higher levels of TNF-α, IL-6, and IL-10 in patients during the early phases of bipolar disorder, where CRP was found to predict the risk of depression (Walker et al., 2014).

Inflammatory biomarkers have the ability to affect antidepressant treatment negatively. Inflammatory biomarkers, such as adiponectin, CRP, leptin, IL1-β, IL6, and TNFα affect the effectiveness of newly developed antidepressants. Investigating the role biomarkers play in depression also has the potential to inform which pharmacotherapies should yield the greatest benefit to which subpopulation suffering from depression (English, Lebovitz, & Griffin, 2010; Strawbridge et al., 2015). Drug development researchers have not y examined the role of biomarkers in identifying populations affected with depression for inclusion in clinical trials (Gaynes et al., 2009). Lopresti et al. (2014) and Strawbridge et al. (2015) might add insight into the relationship between biomarkers and treatment efficacy, thereby improving treatment options and outcomes.

Inflammatory Biomarkers and Treatment Efficacy

Inflammatory biomarkers as a predictor for depression. More research has been conducted on the influence of inflammatory biomarkers (inflammatory cytokines) on mood disorder pathophysiology. These cytokines are also known as proinflammatory mediators (interleukin 1, IL-6, TNF-α, CRP; Sua, 2012; Walker et al., 2014). Furthermore, researchers posited that children at the ages of 10 and 15 years, who have had traumatic experiences between the ages of 1.5 and 8 years, proved to have higher

levels of CRP and IL-6, which was associated with immune activation and symptoms of depression (Sua, 2012; Walker et al., 2014). Higher levels of inflammatory biomarkers have been used to predict the severity of depression and the risk of recurrence in males. Inflammatory biomarkers could be used to predict mood disorder pathology. Increased levels of inflammatory biomarkers related to the progression of mood disorders (Sua, 2012; Walker et al., 2014).

Inflammatory biomarkers used for diagnosis. Bredt et al. (2015) stated that the antidepressants available took weeks to relieve symptoms and that it was often found that the response of patients fluctuated with time. Mood disorders were one of the most common diseases (Bredt et al., 2015). Biomarkers have proved invaluable in the explanation of treatment for diseases, as well as treatment responses of patients (Lopresti et al., 2014). Incorporating inflammatory biomarkers in the diagnoses and selecting of treatment for psychiatric diseases would make a difference in a field that had relied on interviews and questionnaires of patients for evaluation (Lopresti et al., 2014).

Chan et al. (2016) agreed with Bredt et al. (2015) on the available antidepressants not being optimal, and they added that there was only a 50% response rate in patients. With all available aids present, allocating the most effective treatment to patients remained a challenge and happened on a trial and error basis (Chan et al., 2016). Yohannes and Alexopoulos (2014) also posited their concern with the lack of appropriate treatment being allocated to patients diagnosed with MDD and anxiety. The symptoms of these diseases are multifaceted and include social, biological, and behavioral aspects.

Yohannes and Alexopoulos posited that one of the reasons for this problem was the lack of a standardized diagnostic approach for inflammatory biomarkers.

Treatments for depression. Patients often do not respond to treatment for depression; as such, the chances of remission are slim. Ruland et al. (2016) and Sua (2012) postulated the concerns regarding patients with major depressive disorder (MDD) who have proved nonresponsive to several treatments and antidepressants, and who then became treatment resistant as a result of successive unsuccessful treatment. Scholars have highlighted the urgency of new strategies to ascertain personalized and individualized treatment for MDD patients (author, year). Biomarkers that could predict treatment responses would prove a significant tool to allocate the correct treatment (Chan et al., 2016).

To administer the most effective treatment to patients, researchers conducted studies to determine the variables that may predict a patient's response to treatment. Chan et al. (2016) conducted a study investigating the association of 258 potentially predictive inflammatory biomarkers regarding treatment response in 332 MDD patients and showed that a pretreatment immune-endocrine profile could predict a patient's responsiveness to an antidepressant or treatment. This would be of assistance to individualized treatment. Chan et al. investigated tissue inhibitor of metalloproteinases 1, intercellular adhesion molecule 1, apolipoprotein a-iv, endoglin, thrombopoietin, plasminogen activator inhibitor 1, hepatocyte growth factor, complement c3, and insulin-like growth factor-binding protein 2 and their response to Venlafaxine, Imipramine, and other antidepressant drugs. Miller and Raison (2016) stipulated that patients diagnosed with MDD displayed

all the qualities associated with an inflammatory response, which included higher levels of proinflammatory cytokines.

Miller and Raison (2016) stated that there was a correlation between inflammation and depression. Miller and Raison showed that IL-1β, IL-6, TNF, and CRP have the most significant relation to inflammation in patients diagnosed with MDD. Regarding treatment response, the presence of high levels of IL-1β, TNF, and CRP have the most significant predictors. When inflammatory cytokines are introduced to normal controls, they were found to induce the symptoms of depression (Miller & Raison, 2016). Miller and Raison showed that by blocking these cytokines, the symptoms of depression were reduced. Inflammation was correlated with nonresponsiveness to antidepressant treatment (Miller & Raison, 2016). I stopped reviewing here. Please go through the rest of your chapter and look for the patterns I pointed out to you. I will now look at your Chapter 3.

Further studies also sought to determine the correlation between inflammatory biomarkers and the effect on different therapies of depression. Berk et al. (2015) posited that there was often a correlation between depressive disorder and physiological changes, which could affect medical illness, as well as increase proinflammatory cytokines. They sought to determine the impact of religious cognitive behavioral therapy (RCBT) in comparison to conventional CBT (CCBT) and the effect these therapies have on pro/antiinflammatory biomarkers and stress hormones (Berk et al., 2015). The sample consisted of 132 subjects who had been diagnosed with major depressive disorder (MDD) as well as a chronic medical illness. They found that RCBT or CCBT had no significant

effect on change in any biomarkers. CCBT proved more effective in lowering lL-6 in those with low religiosity, and RCBT was more effective in those with high religiosity (Berk et al., 2015). The results of this study were of significance, as these results showed that different therapies related to MDD still had a correlation with inflammatory biomarkers, however insignificant.

Dowlatia et al. (2010) contradicted Berk et al. (2015). The aim of Dowlatia et al.'s (2010) quantitative secondary analysis study was to examine the concentrations of specific cytokines identified in patients diagnosed with a major depressive episode, as the literature suggested a correlation between depression and immune dysregulation, as well as the activation of the inflammatory response system (IRS). After a meta-analysis of the available studies, 24 studies involving unstimulated measurements of cytokines in patients with major depression were included (Dowlatia et al., 2010). Dowlatia et al. (2010) showed significantly higher concentrations of TNF-α and IL-6 in depressed subjects in comparison with control subjects. None of the other cytokines that were examined showed significant differences between depressed and non-depressed subjects. This meta-analytic study was significant, as it strengthened the argument of the current study: Depression correlated with activation of the IRS. The correlation between inflammatory biomarkers and depression was evident and aided further investigation to have a concrete understanding of its relationship (Dowlatia et al., 2010).

Individualized depression therapy. The searches for more accurate treatment with better outcomes for MDD have been vast. As treatment outcomes in patients with MDD are such a pressing problem, the need for predictive variables has increased. Redei

et al. (2014) sought to explore the possibility of a laboratory-based diagnostic tool that could increase the diagnostic accuracy of MDD and determine classifying factors to provide individualized therapy. Furthermore, Redei et al. (2014) sought to determine whether inflammatory biomarkers showed a relationship with treatment outcomes in or if these could be of assistance in such a predictive diagnostic tool. Redei et al. administered cognitive behavioral therapy (CBT) to 32 MDD patients. Blood samples were taken at baseline and at the end of 18 weeks. Redei et al. concluded that blood levels of different transcript panels could predict depression among primary care patients, during a depressive episode or while in remission, or follow and predict response to CBT. The results showed the possible presence of biomarkers in the blood of potential MDD patients. The study was significant, as it correlated with the aim of the study at hand, it and provided premise for further investigation (Redei et al., 2014).

It is well known that the treatments for anxiety disorders are often ineffective, and the variables contributing to this outcome should be examined and determined to assist with individualized treatment. Wolitzky-Taylor, Arch, Rosenfield, and Craske (2012) posited that one must understand under what circumstances, as well as for whom, in the sense of biological composition, treatments were most effective. Wolitzky-Taylor et al. attempted a study to determine the effectiveness of cognitive behavioral therapy (CBT) in comparison to acceptance and commitment therapy (ACT). Eighty-seven patients diagnosed with anxiety underwent 12 weeks of either CBT or ACT, and the patients were measured via a self-report at baseline, after 12 weeks, after 6 months, and after 12 months. The success of CBT was evident when compared to ACT in patients with

medium anxiety levels at baseline who had no additional mood disorders. ACT had more success with patients who had been diagnosed with multiple mood disorders (Wolitzky-Taylor et al., 2012). There was also a correlation between poorer responses to treatment and higher measures of neuroticism at baseline. Comorbidity, race, gender, age, or severity of the disorder were not found predictive of treatment outcomes (Wolitzky-Taylor et al., 2012).

Alternative treatments for depression. As the struggle for successful MDD treatment continues, several alternative treatments have also been studied. Sua (2012) showed significant results for alternative medication, such as omega-3 supplementation. Sua posited that one of the most significant clinical trials on the effect of inflammatory biomarkers and the symptoms of depression included interferon-α-induced depression in patients with chronic hepatitis C. Sua further posited that alternative options for antidepressants were being researched, and it included the antiinflammatory pathway, as well as omega-3 polyunsaturated fatty acids (PUFAs), which were found to have a natural antiinflammatory and antidepressant effect.

Rapaport et al. (2016) examined the effect of inflammatory biomarkers on omega-3 (n-3) fatty acids, and whether it had a mediating effect on patients diagnosed with MDD. One-hundred and fifty-five subjects were recruited, who were diagnosed with MDD (according to the Hamilton Depression Rating Scale). The inflammatory biomarker levels of IL-1ra, IL-6, high-sensitivity hs-CRP, leptin, and adiponectin of the patients were measured at baseline and at the end of the 8 week treatment and placebo (Rapaport et al., 2016). Treatment included eicosapentaenoic acid (EPA)-enriched n-3 and

docosahexaenoic acid (DHA)-enriched n-3 doses per day. Patients were divided into groups of high and low levels of inflammatory biomarkers (Rapaport et al., 2016). Patients who fell in the high inflammatory biomarker level group showed more improvement on EPA when compared to the placebo group. The results for EPA treatment versus placebo were further separated when higher levels of inflammatory biomarkers were present (Rapaport et al., 2016). The patients receiving EPA treatment showed medium decreases on the HRSD scale and showed less response to placebo when compared to patients with low inflammatory biomarker levels (Rapaport et al., 2016). The results of this study are significant, as it implies that the level of inflammatory biomarkers measured in patients may have predictive qualities for treatment outcomes. It also showed EPA treatment was effective in patients with MDD (Rapaport et al., 2016).

Fond et al. (2013) also discovered the effectiveness of polyunsaturated fatty acids on MDD patients through a systematic review of the available literature, without any year or language limitations. Fond et al. specifically researched the efficacy of four major antiinflammatory drugs (PUFAs, COX, antiTNFalpha, and minocycline) on MDD, schizophrenia, and bipolar disorders. Fond et al. found specific significance regarding the effect of these antiinflammatory drugs on MDD. PUFAs were found effective in the treatment of MDD, and antiTNFalpha proved significant efficacy in specifically treatment resistant MDD. The various antiinflammatory drugs available, amidst the side effects, proved valuable alternatives for MDD and treatment resistant MDD (Fond et al., 2013).

Carney, Steinmeyer et al. (2016) also echoed the results of PUFA treatment and its success in relieving the symptoms of depression. Carney, Steinmeyer et al. found that omega-3 supplementation could be an effective treatment for patients with MDD; although, the duration and ratio of treatment depended on baseline omega-3 levels of the patient at hand. Lopresti (2014) tested another alternative treatment using curcumin as an antidepressant. Lopresti sought to determine the antidepressant effects of curcumin on patients who have been diagnosed with MDD. The researcher conducted an 8-week, randomized, double-blind, and placebo-controlled study. Curcumin was administered to patients at a dose of 500 mg, twice daily. For the first 4 weeks of treatment, curcumin, and placebo was found equally effective, but from Weeks 4 to 8, curcumin showed superior antidepressant efficacy. Furthermore, Lopresti sought to determine the potential effect of inflammatory biomarkers on MDD and to evaluate the effects of curcumin on these biomarkers. Results showed that biomarkers could enhance diagnosis, predict treatment progress, and assist in the choice of treatment. Researchers found that urinary leukotriene B4, thromboxane B2, and substance P had changed as a result of curcumin treatment (Lopresti et al., 2014). Treatment efficacy was correlated with higher baseline concentrations of plasma endothelin-1 and leptin. This study provided insight on the predictors of treatment efficacy, as well as evidence of the correlation between inflammatory biomarkers, depression, and the treatment thereof (Lopresti et al., 2014).

Other mental illnesses have also been associated with inflammatory biomarkers, such as anxiety, bipolar disorder, and schizophrenia. Keller et al. (2012) posited that there was an increase of interest on the association between inflammation and schizophrenia,

and also the association of inflammatory biomarkers in schizophrenia treatment. Keller et al. further stated that evidence was increasing regarding the alternative treatments for schizophrenia, including antiinflammatory treatments. They predicted that the research on this topic would expand even more within the next few years (Keller et al., 2012).

Loebel et al. (2014) conducted a study on the effects of lurasidone (antipsychotic agent) in conjunction with lithium or valproate as adjunctive therapy in patients diagnosed with bipolar and depression. The sample, used for this study, was focused on patients who have not responded to monotherapy (Loebel et al., 2014). The trial included 6 weeks of the abovementioned therapy for 183 patients and placebo for 165 patients. The Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions scale was used to measure depression and bipolar severity at baseline and at the end of the trial (Loebel et al., 2014). The effects of lurasidone treatment were significant in relieving depression as well as bipolar when compared to placebo. There were also significant improvement on anxiety symptoms, as well as an increase in quality of life (reported by patients) and functional impairment (Loebel et al., 2014).

Anderson et al. (2012) investigated another treatment option for treatment resistant depression (TRD). Deep brain stimulation (DBS) was found effective on symptoms associated with movement disorders. Anderson et al. sought to determine the effectiveness of DBS on patients with TRD. The study sample was limited, but according to the literature, there had been great success in the reduction of depressive symptoms, as well as elevated rates of remission for TRD patients (Anderson et al., 2012). Although the encouraging results, there remained a lack of understanding in the mechanisms

providing the success. More studies should be conducted to identify the variables at play (Anderson et al., 2012).

Depression is often found as a comorbid disease in patients with inflammatory illnesses. A correlation between depression and inflammatory bowel disease had surfaced because recent research has proven depression to be significantly associated with activated immune-inflammatory, oxidative, and nitrosative stress (IO&NS) pathways (Martin-Subero, Anderson, Kanchanatawan, Berk, & Maes, 2015). Martin-Subero et al. (2015) also found that there was an increase in depression manifestation in IBD patients, which causes increased morbidity, as well as lower quality of life. The cause of depression manifestation in IBD patients related to an increased level of proinflammatory cytokines. It seemed that the mechanics of depression and IBD overlap, which could explain this phenomenon. Martin-Subero et al. further stated that this could have an implication on the treatment for IBD when depression was also present in a patient (Martin-Subero et al., 2015).

One could conclude that several treatments existed for the treatment of depression, and yet the outcomes of these treatments were not full proof. Martin-Subero et al. (2015) agreed that more research should be conducted to determine the variables, influencing treatment outcomes, to revolutionize treatment allocations, which would be most effective according to specific patients. The heterogeneity of depression remained a reality, and researchers should focus on the cause of it to determine the solution (Kessler et al., 2016).

Inflammatory Biomarkers and Remission Outcomes

When patients are diagnosed with depression, it is expected that the process to remission is lengthy, including several types of treatment including antidepressant drugs and therapy, and yet remission is still not guaranteed. Fava and Rush (2006) posited that most patients diagnosed with MDD never reached remission. The severity of depression in these patients are often much worse compared to patients who are found to remit. Several treatments and antidepressant drugs are administered to these patients to find an appropriate and effective treatment to reduce the symptoms, with remission as a long-term goal. Fava and Rush felt that not enough controlled studies had been completed on the effectiveness of treatments, and clinicians should be more cautious when administering treatment to give their patients the highest chance of remission. Brent et al. (1998) found that clinical remission had a positive correlation with self-reported depression. One could assume that self-perspective played a role in the success of treatment as well as the chances of remission.

Remission is subjective. The state of remission experienced by patients may be subjective. This significantly increases the diagnoses and correct treatment of MDD patients. Zimmerman et al. (2012) posited that the definition of remission from depression was not well defined. Zimmerman et al. examined the amount depressed patients, who were in remission according to the HRSD, who did not agree that they were in remission. Zimmerman et al. further investigated the demographical and clinical differences of the patients who did or did not agree with their own remission status. In addition, 274 patients were interviewed over more than a year. The results showed that 77

of 140 patients who were remitted did not agree with their remission status (Zimmerman et al., 2012). The patients considered themselves in remission and had considerably lower levels of depression when compared to the patients who did not consider themselves in remission. Patients in remission proved to have considerably higher life quality and more functionality. Patients also had higher levels of mental health, better coping ability, and were less likely to report dissatisfaction in their mental health. The study proved that symptoms should not be relied on independently (Zimmerman et al., 2012). A closer eye should be kept on remission status, and treatment should be adjusted accordingly. Zimmerman et al. (2012) demonstrated the heterogeneity of depression, the treatments thereof, and the misconceptions of remission with their findings.

A variable that may also influence MDD patients' state of remission is their perspective of remission (Zeng et al., 2016). An extensive quantitative study was conducted in China to determine the perspective of remission in patients not submitted to clinics (Zeng et al., 2016). The design of the study was prospective, multi-centered, and observational. The sample included 9855 patients who were assessed at baseline, Week 2 and Week 4, using the 17-item Hamilton Rating Scale for Depression (HRSD), as well as the Remission Evaluation and Mood Inventory Tool (REMIT). The patients' symptoms and general sense of wellbeing and mental health were assessed (Zeng et al., 2016). The results showed that 91.3% of patients experienced medium to intense depression. Zimmerman et al. (2013) found that definite improvement was reported after 4 weeks of treatment in terms of symptoms, as well as general sense of wellbeing. Zimmerman et al. determined that more focus on the wellbeing and mental health status of patients would

provide the patients themselves, as well as clinicians with wider perspective on the health status of patients.

As the state of remission may be subjective, another study sought to determine the validity of models that measure depression and remission. A study conducted on 153 patients with MDD to determine the validity of the Remission from Depression Questionnaire (RDQ) in comparison to the Quick Inventory of Depressive Symptomatology (QIDS) and 17-item Hamilton Rating Scale for Depression (HRSD) found that all three of these measures proved correlated and quite accurate (Zimmerman et al., 2013). The patients were assessed at baseline and after 4 months, and the researchers postulated that the use of the RDQ might provide more insight on the remission status of patients, and physicians should use this to their advantage (Zimmerman et al., 2013).

Diagnostic tools to administer appropriate treatment. Determining predictors of treatment response would significantly increase the chance of remission for patients with MDD. Carney, Freedland, Steinmeyer, Rubin, and Rich (2016) sought to determine if there was a correlation in the predictors for treatment response for patients with major depressive episode, as well as patients with coronary heart disease (CHD). One-hundred and fifty-seven patients with CHD and major depressive episode were treated with CBT, with or without an antidepressant over 16 weeks. At the end of the 16 weeks, over 50% of the subjects were in remission. The researchers found that depression outcomes were predicted by severe depression at baseline, stressful life events during treatment, and the completion of CBT homework assignments (Carney, Freedland et al., 2016). Carney,

Freedland et al. (2016) concluded that patients who were under severe stress were less responsive to treatment for depression. This study was significant, as it also showed success with CBT treatment. Furthermore, it gave insight on why patients might be less responsive to treatment, and clinicians should take note of this before commencing with treatment of MDD patients (Carney, Freedland et al., 2016).

Dodda et al. (2014) aimed to examine the gradient boosted model (GBM). The GBM is a statistical technique that can identify and measure variables that influence treatment outcomes when it is applied to clinical trial data. Dodda et al. applied the GBM to 12 clinical trials, totaling 4987 human subjects. The subjects included in the trial had been diagnosed with an acute depressive episode, and they had been treated with duloxetine, an SSRI, or placebo to predict treatment remission. After the GBM had been applied, significant differences could be measured regarding treatments and which variables associated with remission. Dodda et al. concluded that the GBM provided greater flexibility regarding the identification of patient variables that predicted remission, and it might give insight to individualized treatment options. The information gained from this study furthered the argument on the mystery of the various treatments available for MMD and the various treatment outcomes that were experienced by individuals (Dodda et al., 2014).

Rush et al. (2012) postulated that MDD was often chronic, recurring, or both. The researchers sought to determine whether MDD was chronic, recurring, or both and whether it correlated with long-term treatment outcomes. Their cohort study included patients across all ages who were diagnosed with MDD. The treatment groups included

389 chronic and recurring MDD patients, 257 chronic non-recurring MDD patients, 1614 non-chronic recurring MDD patients, and 387 non-chronic and non-recurring MDD patients. The aim was for the patients to remit or at least improve after 14 weeks of citalopram treatment, including follow-up treatment for 12 months. In addition, 85% of participants were administered a chronic or recurrent course and 15% had both. Chronic MDD had a correlation with increased sociodemographic disadvantage. Recurrent MDD correlated with earlier age diagnosis and genetic history of depression, as well as substance abuse. Chronic MDD associated with slow response to treatment and low remission rates. Higher risk of relapse associated with the chronic and recurring MDD treatment group. Rush et al. determined that chronic recurring MDD might be predictors of long-term MDD treatment outcomes. Rush et al. showed the severity for the need of more research regarding treatment outcomes to ensure remission for all patients.

Treatment Resistant Depression

Remission status is not a guarantee, as several MDD patients have proven to be unaffected by several treatments, and successful treatment does not necessarily result in remission. For example, Gaynes et al. (2009) sought to determine which treatments proved most effective for patients diagnosed with MDD who have proven to be unaffected by treatment, or whose symptoms did not go into remission through a large-scale practical clinical trial. Participants were recruited from psychiatric and primary care clinics. After recruitment, participants began on citalopram. Clinic physicians followed an algorithm-guided acute-phase treatment through five visits over 12 weeks with the patients. Patients whose depression had still not remitted after each sequence were

eligible for further trials. They concluded that none of the medication administered had a significant effect on the patients (Gaynes et al., 2009). It was clear that several steps would be needed for patients to go into remission successfully, as the remission rates were even lower than expected for the trial. Remission also became a less likely outcome after two vigorous trials, and even more complicated medication regiments would be needed to successfully achieve remission (Gaynes et al., 2009). The evidence of more complicated treatments was minimal. This study proved the need for even more research and clinical trials to make discoveries on the treatment of MDD.

Successful treatment administration. Regarding successful treatment administration, some researchers have suggested predictive analytic models. Kessler et al. (2016) posited that data predictive analytic models might be more helpful to assist physicians in making decisions on treatment when compared to the lack of information of biomarkers as predictors of treatment outcome. Kessler et al. investigated the validity of prediction based on symptoms and clinical features that can be easily assessed. Kessler et al. looked at existing research to determine the validity of these factors to predict treatment outcomes to assist in individualized treatments. Kessler et al. further expressed the need of protocol that could collect data over time to determine the predictors of the heterogeneity of MDD and the response of patients to treatment. The data collected should be used to focus on the treatment response of patient populations, which remained a mystery (Kessler et al., 2016).

According to McGrath et al. (2013), less than 40% of patients who have been diagnosed with MDD and have received initial treatment, achieved remission. McGrath

et al. posited that the identification of a biomarker that could predict treatment outcomes would make a considerable impact on health care. The brain glucose metabolism of 65 patients (male and female, ages 18-60 years with untreated MDD) was measured at baseline, and the patients were treated with escitalopram oxalate or cognitive behavior therapy over 12 weeks. Remission was measured through HDRS. Patients who were not in remission after the first 12 weeks were opted for treatment for another 12 weeks, with treatment including escitalopram, as well as cognitive behavior therapy (McGrath et al.. 2013). From 65 patients, 38 showed the following clear results: 12 patients who achieved remission through cognitive behavior therapy and nine nonresponders, as well as 11 patients who achieved remission through escitalopram and six nonresponders (McGrath et al.. 2013). The researchers concluded that the insula metabolism-based treatment-specific biomarker was identified in this study, and it might provide the first objective marker to assist in treatment selection for patients with MDD (McGrath et al., 2013).

Increasing the chance of successful treatment. Aside from the fact that accurate predictive variables have not been found to determine treatment outcomes before treatments are administered, alternative methods to increase the chances of successful treatment have been researched. Fava et al. (2015) conducted a randomized, double blind, and placebo-controlled trial to investigate the efficacy of CP-601,927. CP-601,927 is an amplifying agent of antidepressant drugs in patients with MDD that has insufficient response to selective serotonin reuptake inhibitors (SSRIs). Fava et al. did not find a significant difference in the relief of depression from baseline to Week 14 when the CP-610,927 treatment was compared to placebo. Fava et al. further found an association

between increased BMI and specific biomarkers, which suggested that baseline leptin, affected treatment outcome significantly. Fava et al. concluded that CP-601,927 was not an enhancer of antidepressants, as no difference was observed when compared to placebo in MDD patient that had an insufficient response to SSRIs.

Jani et al. (2015) provided valuable insight with their review on the literature regarding biomarkers and the ability to predict depression severity, treatment response and remission status, as well as the occurrence of other illnesses. Jani et al. postulated that the diagnosis of depressive symptoms was difficult to establish in primary care, as that was where the majority of depression patients were being cared for. Jani et al. stated that comorbidity was the cause. Many studies have included biological pathways in their studies on the treatment of MDD, and yet there has not been conclusive evidence on accurate predictive biomarkers (Jani et al., 2015).

Patients with heart failure with comorbid depression who could achieve remission proved to have greater improvement in social function, physical function, and quality of life (Xiong et al., 2012). It could thus be concluded that more studies were definitely needed to increase the chances of remission. There were variable factors influencing chances of remission (initial vigorous ineffective treatment, previous substance abuse, late diagnoses), and more research was needed to determine the biomarkers responsible for this phenomenon (Xiong et al., 2012). Physicians should also take greater care before administering a specific course of treatment, as the extent of several treatments and drugs could result in a patient becoming treatment resistant (Xiong et al., 2012).

Inflammatory Biomarkers and Treatment Responses Mediated by Age, Race, and Gender

Wolitzky-Taylor et al. (2012) posited that it was of utmost importance to understand what circumstances, as well as for whom, biological composition treatments were most effective. Wolitzky-Taylor et al. found that there was a correlation between poorer response to treatment and higher measures of neuroticism at baseline. Comorbidity, race, gender, age, or severity of the disorder was not found predictive of treatment outcomes (Wolitzky-Taylor et al., 2012). In this section, I look at the current literature in the light of age, race, and gender as mediators of treatment response.

Age. Further proof of the association of depression and its correlation with inflammatory biomarkers has derived from suicide victims. In an investigation of adolescent suicide victims, higher levels of IL-1β, IL-6, and TNF-α were measured in comparison to normal controls, further aiding the correlation between inflammatory biomarkers and depression (Miller & Raison, 2016; Walker et al., 2014). Higher levels of inflammatory cytokines (TNF-α, IL-1β, IL-6, and IFN-γ) were discovered in pediatric patients experiencing first-episode psychosis (Walker et al., 2014). However, this age specific evidence did not prove that age was a mediator, but merely furthered the premise of a correlation between MDD and inflammatory biomarkers.

As stated previously, depression is often found as comorbidity in patients with other inflammatory illnesses. There is also inflammatory treatment for illnesses, which may result in depressive symptoms in the patients receiving the therapy. Hauser et al. (2002) concluded that Interferon (IFN) therapy associated with the development of MDD

in patients with hepatitis C (HCV). Hauser et al. sought to determine whether IFN-induced MDD could be treated effectively with open-label antidepressants (selective serotonin reuptake inhibitors/SSRIs). Hauser et al. also examined, among others, the mediation of age and gender. Thirteen out of 39 HCV patients on IFN therapy became depressed and were treated with citalopram, a SSRI antidepressant. Variables, such as age, gender, past history of MDD, or substance use, did not mediate the outcome. There were significantly lower numbers of African American patients who had become depressed. It took an average of 12.1 weeks for patients to develop MDD from IFN therapy. Eleven of the depressed patients responded positively to the treatment administered. Hauser et al. concluded that MMD was a common risk factor for HVC patients who were being treated with IFN therapy. Doctors should be alert for the manifestation of MDD in their HVC patients. Citalopram proved an effective treatment for IFN-induced MDD patients (Hauser et al., 2002).

Depression is known to affect population groups of various ages, and yet the research on treatments available and treatment outcomes for children and adolescents remains limited. Luby (2013) posited that there was evidence of depressive disorders and anxiety in children as young as 3 years of age. The development of age appropriate treatment is lagging behind. After comprehensive research, the consensus was that adapted forms of cognitive-behavioral therapy had been successful in a small randomized controlled environment (Luby, 2013). The adaptive form of cognitive-behavioral therapy included the involvement of primary caregivers, as well as cartoon-based material. Furthermore, adapted forms of Parent Child Interaction Therapy also appear promising

for the improvement of child depression and anxiety. Direct treatment of the youngest children within a family seems to be necessary for a long-term effect (Luby, 2013). This study provided insight to the available therapies for preschool children diagnosed with anxiety and depression. This added to the premise of the current study: Age might be a mediator of therapy outcomes for the treatment of depression.

Allison, Nativio, Mitchell, Ren, and Yuhasz (2014) commented on the lack of knowledge in the detection of depression in children who are still in school. The benefit of early detection of mood disorders in children is prompt treatment. Mood disorders affect children's' schoolwork, and the disease may worsen if not detected timeously (Allison et al., 2014).

Cipriani et al. (2016) agreed with Allison et al. (2014) and Luby (2013). They posited that MDD was one of the most common mental disorders, but it was yet to be determined which antidepressant and/or treatment was most effective. Cipriani et al. focused on 34 trials, 5260 participants (children and adolescents) and 14 antidepressant treatments. After research, Cipriani et al. decided that trials of amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine would be included. Trials that included treatment-resistant patients, treatment duration of less than 4 weeks, or a sample size of less than 10 patients were excluded (Cipriani et al., 2016).

The results of the data analyses showed that only fluoxetine was statistically more effective than placebo for treatment efficacy (Cipriani et al., 2016). Fluoxetine proved more tolerable compared to duloxetine and imipramine. Discontinuations, because of side

effects, happened more often for imipramine, venlafaxine, and duloxetine when compared to placebo. The conclusion was that none of the drugs seemed extremely effective, although fluoxetine proved the best choice compared to the other antidepressants (Cipriani et al., 2016). The results of the study showed the ineffectiveness of drugs being administered to children and adolescents, and proved that there was a lack of information on treatments for children and adolescents diagnosed with MDD (Cipriani et al., 2016).

Mills, Scott, Wray, Cohen-Woods, and Baune (2013) postulated that the relationship between depression and cytokines in adults was evident, but that the research was lacking on this relationship for adolescents. Mills et al. reviewed the available literature on the relationship between cytokines and depression in adolescents and investigated how cytokines related to adolescent depression concerning neurobiological theories of depression. After extensive research, 18 studies were chosen, which had measured depression and cytokines in adolescents (Mills et al., 2013). The analyses of the studies showed that adolescents diagnosed with depression expressed age-specific characteristics of the immune and inflammatory system, more specifically, NK cell activity and proinflammatory cytokines. Mills et al. (2013) concluded that neurodevelopment, hormones, stress, and trauma influenced the role of cytokines in adolescents with depression. Neurobiological differences might exist between adolescent MDD and adult MDD. This aided the hypothesis of the study at hand that age might be a mediating factor in the treatment of MDD. Mills et al. stated that more information on this subject could lead to better treatment of MDD for adolescents.

Several studies have been conducted on the treatment responses of adults to various treatments of MDD. Few studies, up to this point, have been devoted to determining the correlation between age and the treatment outcomes of the treatment available. Brent et al. (1998) sought to determine the predictors of treatment outcomes across several different treatments, and the predictors associated with the different responses to treatment in adolescents. Brent et al. included a sample of 107 subjects (13 to 18 years old) who have been diagnosed with major depression. The subjects were assigned 1 of 3 different psychosocial treatments (12 to 16 sessions). The treatments included cognitive-behavioral therapy (CBT), systemic-behavioral family therapy, or nondirective supportive therapy. The results showed that clinical referral, as opposed to subjects responding to advertisements, predicted continued depression, and were mediated by hopelessness (Brent et al., 1998). Comorbid anxiety disorder, higher levels of cognitive distortion and hopelessness were also determined as predictors of depression. Clinical remission had a positive correlation with self-reported depression. Differential treatment efficacy was predicted by comorbid anxiety and maternal depressive symptoms (Brent et al., 1998). CBT was more effective when compared to the other therapies used, even with the mentioned predictors present. Brent et al.'s (1998) study was significant to the study at hand, as it provided insight on the results of different therapies, and which of the therapies would likely be the best option for difficult-to-treat patients.

A lack of significant research on the effects of depression on the elderly was also determined. As stated previously, depression does not discriminate based on age. A cross-sectional study conducted in Stockholm, Sweden aimed to determine the

prevalence of depression in patients over the age of 60 without dementia (Karlsson, Johnell, Sigström, Sjöberg, & Fratiglioni, 2016). Karlsson et al. (2016) found that the prevalence of depression was 5.9%. Moreover, 8.3% of the sample was prescribed as an antidepressant, and 0.9% was treated with psychotherapy. Karlsson et al. concluded that depression in old age often remained untreated, as patients were not diagnosed at all or were even misdiagnosed. As a result, these patients often received inappropriate treatment (Karlsson et al., 2016). The study did not include age as a mediator for depression treatment, although it did provide information on the lack of depression treatment for elderly individuals with MDD.

Using age as a predictor of treatment outcomes in the administration of MDD treatment has not been proven definitively. Maes, Mihaylova et al. (2012) posited that MDD associated with cell-mediated immunity (CMI), increased neopterin levels, and higher levels of proinflammatory cytokines (PICs). They speculated that PICs might cause depressive, melancholic, and chronic fatigue (CF) symptoms. In addition, 85 MDD patients and 26 normal controls were used for the study. The serum levels of these patients were measured, and their severity of depression was measured with the Hamilton Depression Rating Scale (HDRS) and severity of CF with the Fibromyalgia and Chronic Fatigue Syndrome (FF) Rating Scale (Maes, Kubera et al., 2012). A positive relationship was evident between neopterin, the PICs, and amount of depressive episodes. Neopterin and TNFα were correlated with melancholia and CF. Melancholia was predicted by the HDRS and neopterin. CF was predicted by age, the FF score, and TNFα (Maes, Kubera et al., 2012). Inflammatory responses may be accompanied by the onset of depression, as

well as depression symptoms. Previous depressive episodes could enhance PIC responses and increase the risk of new depressive episodes. Inflammation could cause the reoccurrence of depression (Maes, Kubera et al., 2012). The results of this study showed further proof of the effect that inflammatory biomarkers have on depression (Maes, Kubera et al., 2012). It also showed merit for the hypothesis of this study that treatment responses might be mediated by age.

From another perspective, of the preventative nature, early detection of depression may result in treatment that is more effective and a higher chance of remission. Khandaker, Pearson, Zammit, Lewis, and Jones (2014) aimed to determine whether high levels of inflammatory biomarkers in children were predictors of mood disorders later in life. Their study involved 4500 individuals aged 9 years. The serum levels of the participants were measured at Age 9, and again at 18. The Clinical Interview Schedule–Revised (CIS-R) and Mood and Feelings Questionnaire (MFQ) were used to evaluate the participants. The results showed a significant higher risk for the children with high baseline inflammatory biomarkers to have depression at the age of 18. Khandaker et al. (2014) also found that higher levels of IL-6 levels at baseline could results in psychotic disorder at Age 18. The researchers concluded that inflammatory biomarkers might improve current methods of intervention and even provide preventative measures. Khandaker et al. also accumulated the high likelihood of comorbidity between heart disease, diabetes mellitus, depression, and schizophrenia to inflammatory biomarkers.

In relation to the above mentioned study, a lack of diagnosis, and as a result treatment, would result in a higher percentage of fatalities. Czyz, Horwitz, Eisenberg,

Kramer, and King (2013) posited the challenge of personal barriers that prevented suicidal adolescents from seeking help from professionals. Czyz et al. sought to determine the demographical and clinical variables that might influence the abovementioned challenge. The 165 participants were found via a web-based treatment linkage intervention questionnaire. The barriers identified were the perception of the students that they do not need treatment (66%), lack of time (26.8%), and preference for self-management (18%). Stigma was mentioned by only 12% of students (Czyz et al., 2013). Efforts to promote professional help to suicide risks should be aimed at removing these barriers to be successful.

Most of the studies reviewed were only concerned with the lack of identification in late life depression, as well as the lack of early detection, the lack of treatment available for preschool children, and the increased levels of inflammatory biomarkers in suicidal adolescents, and yet few of the studies specifically investigated age as a mediator (Allison et al., 2014; Wallace et al., 2012). The studies on age as a mediator for depression and treatment outcomes remain inconclusive. More studies are needed to look at this specific variable; although, that may be increasingly difficult with the amount of treatments available and the lack of response prediction (Damián, Pastor-Barriuso, Valderrama-Gama, & de Pedro-Cuesta, 2016).

Race. As discussed previously, Hauser et al. (2002) determined that variables, such as age, gender, history of MDD, or substance use, did not mediate the outcome, but that significantly lower numbers existed of African American patients who had become

depressed. The research on race as a mediator of treatment outcomes is extremely limited. In this section, I examine the outcomes of the research obtained on this matter.

Any predictors of treatment outcomes that may be related to race may assist health care providers to administer the correct treatment for MDD from the first diagnoses. Adamsa et al. (2014) sought to determine the differences in the process of clinical depression of African American and African-Caribbean patients in comparison with White patients in the United States and England. The researchers investigated racial disparities that might affect depression treatment. Moreover, 108 doctors were included in the study and were asked to describe their thought processes after viewing video-recorded simulated patients with identical symptoms of depression. Adamsa et al. made use of the CliniClass system to analyze the data. This system provides the capturing of information about microcomponents of clinical decision-making and assists in the detailed analysis of diagnostic, intervention and management decisions of doctors. Actors portrayed the several different races, as well as male and female patients in these recordings. The doctors were randomly selected stratified by country (United States *vs*. England), gender, and years of clinical experience (less *vs*. very experienced). The findings did not show significant bias among the races under study, except for the outcomes expected and the treatments available for African Americans in comparison with White American patients in the United States (Adamsa et al., 2014). Adamsa et al. (2014) concluded that great clinical uncertainty existed in diagnosing depression amongst Black patients in comparison with White patients in England. The evidence suggested that more attention was paid to Black patients physical rather than psychological ailments

to reach diagnosis in both countries. This implied that doctors in both countries have a less well developed mental model of depression for Black compared with White patients (Adamsa et al., 2014).

When administering antidepressant treatment, bias might play a role for some health care providers. Pickett, Greenberg, Bazelais, and Bruce (2014) sought to determine if race or ethnicity influences the treatment of depression with the use of cross-sectional analyses of administrative data. The study was conducted in a healthcare facility in New York, and the participants included 3744 patients over the age of 65 who had been diagnosed with depression. The severity of depression in these patients was measured via the Measurements Patient Health Questionnaire. All other data used for the study were obtained from the patient electronic medical record. The results showed that 6.52% of the patients included in the study diagnosed positive for depression, 11.11% screened positive for depression with the use of the questionnaire, and 13.39% were prescribed with antidepressant drugs (Pickett et al., 2014). The chances of an antidepressant prescription among those who screened positive for depression were 0.42 for African Americans and 0.49 for Hispanics in comparison with Caucasians. The findings suggested that there remained discrepancies among depression treatment for elderly patients across races, with Caucasians being favored (Pickett et al., 2014).

In terms of treatment response across races, little information was available, as few studies investigated the probability thereof. Murphy et al. (2013) conducted one such study, and they concluded that Black participants had a worse response to antidepressant treatment when compared to White participants. The discrepancies remained evident,

even after socioeconomic and initial clinical factors were accounted for in the study. According to Murphy et al., some researchers contributed these discrepancies to genetics, but none have determined the reason for these discrepancies. Murphy et al. used genome-wide single-nucleotide polymorphism (SNP) data to examine the independent characteristics of race and genetics. Murphy et al. conducted secondary data analyses that included 1877 patients who were treated with citalopram over the course of 10 weeks. From the 1877 sample size, 1464 participants were White, 299 were Black, and 114 were other or mixed race. The researchers made use of structural equation modeling to examine the direct and indirect influences of and possible predictors of response to treatment and change was observed using the Quick Inventory of Depressive Symptomatology (QIDS) score (Murphy et al., 2014). The severity of depression was measured at baseline and after 10 weeks of treatment. The results showed a significant effect of socioeconomic factors, clinical factors, race, and anxiety on the response to treatment (Murphy et al., 2014). These factors were found as predictors of the treatment response of patients. In contradiction, no direct effects of genetic ancestry were found. Genetic African ancestry predicted poorer treatment response in all models. Genetic ancestry, rather than self-reported race, provided significant information on the residual differences. The findings emphasizes the need for more clinical trials, especially ones including more African-American patients (Murphy et al., 2014).

The available studies on depression treatment across various races were particularly limited, and more research investigating race as a variable would add to the literature. Only a few sources had observed poorer response to treatment in Black

patients. The above studies did not necessarily attempt to determine race as a variable for the effectiveness of depression treatment, but rather stated the lack of or differential treatment across races.

Gender. Miller and Raison (2016) posited that depression in women increased significantly when compared to men. This phenomenon was even more significant during the reproductive years. Recent studies have shown women to be more prone to the effects of inflammation on behavior, which resulted in more significant symptoms of depression. Women are also believed to be at higher risk for depression induced by doses of interferon-α (IFNα). Being prone to depressive symptoms caused by inflammation, these symptoms might have provided women with more protection to fight infection and heal wounds as well as avoiding illness. Inflammation could have negative effects on reproduction, as it reduced fertility and impaired lactation. This could provide explanation as to the higher increase in depression in women when compared to men, and yet it might have helped women to cope with and avoid pathogens and the inflammation related to them with depression being the price they pay (Miller & Raison, 2016).

In agreement with Miller and Raison (2016), the following study also found that women were more prone to the onset of depression. Bengtson et al. (2016) conducted a study to determine the discrepancies of depression treatment effectiveness across HIV-infected patients from different genders and races. 31,000 HIV-infected adults were included in the study and were obtained from eight different clinics where they have been diagnosed with depressive symptoms within 1 month of HIV diagnoses. Bengtson et al. (2016) measured the depressive symptoms of the patients using the Patient Health

Questionnaire-9 (PHQ-9). Antidepressant treatment was defined as a patient having a current antidepressant prescription. Evidence-based antidepressant treatment was considered if treatment changes had been observed from a person's most recent PHQ-9, in accordance with clinical guidelines. Bengtson et al. used multivariable Cox proportional hazards models to determine correlations between gender, race, and the depression outcomes. Bengtson et al. determined that 47% of the sample showed an indication for antidepressant treatment. Bengtson et al. study found significant drop-offs along the depression treatment cascade. The results showed definite discrepancies across all variables. Women were found as more prone to show the need for antidepressant treatment, receive antidepressant treatment, and receive evidence-based antidepressant treatment, even after accounting for race. Blacks, Hispanics, and other races were less likely to seek antidepressant treatment, in comparison to White patients (Bengtson et al., 2016).

Dementia, an inflammatory illness, has also been found correlated with depression, especially in elderly patients, as they are more often associated with dementia. Matsushima et al. (2015) posited that the risk of depression in dementia patients was rising, and inflammation presented in both illnesses might be the reason. The researchers conducted a study on 64 patients over the age of 65 who have not been diagnosed with dementia and who were not living in any healthcare facility. The inflammation levels of interleukins (IL)-1β, IL-2, IL-6, soluble interleukin-2 receptor (sIL-2R), soluble interleukin-6 receptor (sIL-6R), high sensitivity C-reactive protein (hsCRP), and tumor necrosis factor (TNF)-α of the patients were measured at baseline, as

well as after 3 years. The severity of depression was measured using the Beck Depression Inventory (BDI) and cognitive decline for dementia was measured with the Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB), and Clock Drawing Test (CDT), also at baseline and follow-up. The analyses were deemed appropriate across all ages, genders, and educational levels (Matsushima et al., 2015).

The results of the cross-sectional analysis, proved soluble IL-2 receptor (sIL-2R) associated only with men, according to the MMSE score at baseline (Matsushima et al., 2015). The longitudinal analysis, however, showed none of the inflammatory biomarkers correlated with depressive symptoms or cognitive decline. The findings showed that sIL-2R associated with current cognitive function in men, yet none of the inflammatory biomarkers predicted future depressive state or cognitive decline in the community-dwelling healthy older sample (Matsushima et al., 2015). The results of this study showed no evidence of gender as a mediator in depression treatment (as treatment was not part of the study), and yet also disagreed with the hypothesis of inflammatory biomarkers being a predictor in mental illnesses (Matsushima et al., 2015).

Cardoso et al. (2014) postulated on recent studies that had evaluated the role of brain-derived neurotrophic factor (BDNF) in mood disorders. Cardoso et al. sought to determine the differences of serum neurotrophic factors (BDNF, NGF, and GDNF) in patients diagnosed with depression and normal controls. Cardoso et al. also stratified the results according to gender in a sample of young patients aged between 18 and 29. The design of their study was cross-sectional. They used the ELISA method to measure the concentrations of neurotrophic factors. The severity of and length of depression was

determined by the Structured Clinical Interview and the 17-item Hamilton Rating Scale for Depression (HRSD). The levels of BDNF and GDNF measured were found to be lower in major depressive disorder (MDD) patients compared to controls. The levels of NGF measured were higher in MDD patients versus controls. BDNF was correlated with the duration of disease only in women. NGF was associated with the severity of depressive symptoms, anxiety and disease duration in women in comparison to men, but was also correlated with disease duration in men (Cardoso et al., 2014). The finding showed that significant neurochemical differences in NGF and BDNF correlated with the clinical features of MDD when patients were stratified by gender (Cardoso et al., 2014).

The research shows that treatment efficacy is not significantly mediated by age, or race, but that variables, such as self-concept, perspective of wellbeing, and self-awareness, may be more likely to mediate treatment outcomes and remission. However, some of the studies did suggest that Blacks were less likely to have a positive response to depression treatment, and other studies also showed evidence that women are more prone to the manifestation of depression. It can, however, still be concluded that the outcomes of treatment is very difficult to predict, with so many variables at play. More studies are needed to gain concrete knowledge on the subject.

Summary and Conclusions

Current interventional pharmaceutical therapies targeted for depression are not considered adequate enough to achieve sufficient remission following treatment (Hashimoto, 2015; Slavich & Irwin, 2014; Wray et al., 2012). Depression yields a notable burden in terms of adverse symptomatology, decreased productivity, increased morbidity,

and also contributes to rising mortality as a result of suicide (Wray et al., 2012). Depression is one of the most significant health challenges worldwide, and is one of the biggest contributors of health disability and costs. It has been profusely stipulated that depression is heterogeneous, and current diagnostic measures rely on symptoms which has been found to be unreliable and inconsistent (Jani et al., 2015). Incorporating inflammatory biomarkers in the diagnoses and selecting of treatment for psychiatric diseases would make an immense difference in a field that mainly relied on interviews and questionnaires of patients for evaluation (Lopresti et al., 2014).

There are resources providing evidence of the relationship between inflammatory biomarkers and depression, yet there remains a lot to be discovered regarding the effects of biomarkers on treatment efficacy. Depression remains a heterogeneous disease. Specific biomarkers and the extent of their influence on treatment responses and remission outcomes are yet to be determined, as well as whether a definite mediation is found from variables such as age, race and gender. There is less research showing the effect of inflammatory biomarkers in adolescence, while the effect of inflammatory biomarkers is believed to happen at key stages in a patient's life, such as adolescence. The literature shows evidence of higher levels of TNF-α, IL-6, and IL-10 in patients during the early phases of bipolar disorder, where CRP has been found to predict the risk of depression (Walker et al., 2014). The literature also showed possibilities for alternative treatment that should be explored further. The efficacy of antiinflammatory drugs has proved successful in several studies (Fond et al., 2013; Rapaport et al., 2016; Sua, 2012)

When patients are diagnosed with depression, it is expected that the process to remission is lengthy, including several types of treatment including antidepressant drugs and therapy, and yet remission remains not guaranteed. Fava and Rush (2006) posited that most patients diagnosed with MDD never reached remission. The severity of depression in these patients are often much worse compared to patients who are found to remit. Often, several treatments and antidepressant drugs are administered to these patients to find an appropriate and effective treatment to reduce the symptoms in the least, with remission as a long-term goal.

The current study might provide valuable insight into the relationship between biomarkers and treatment efficacy, thereby improving treatment options and outcomes (Lopresti et al., 2014; Strawbridge et al., 2015). More evidence on inflammatory biomarkers and the relationship with various illnesses would provide great insight for individualized treatment, resulting in a lower rate of patients becoming treatment resistant, greater remission possibilities, and a reduction in the mortality rate across populations. Chapter 3 contains the methodology involved in this quantitative secondary analysis study.

Chapter 3: Research Method

The purpose of this quantitative, secondary data analysis was to determine if there was a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who demonstrated a previous lack of remission. In this chapter, I expound on the research methodology and design that was introduced in Chapter 1. The chapter includes details relating to the study methodology, the data analysis plan, and threats to the validity of the study. The chapter concludes with a summary.

Problem Statement

Current interventional pharmaceutical therapies targeted for depression are not considered adequate enough to achieve sufficient remission following treatment (Hashimoto, 2015; Slavich & Irwin, 2014; Wray et al., 2012). Depression yields a adverse symptomatology, decreased productivity, and increases in morbidity (Wray et al., 2012). Moreover, depression also contributes to the facilitation of rising mortality as a result of suicide (Wray et al., 2012). In clinical trial data on outcomes in depression, scholars have demonstrated that achievement of remission is decreasing (Gartlehner et al., 2016; Gaynes et al., 2009; Steidtmann et al., 2013). There is a need to implement strategies that adequately stratify subpopulations to determine among which groups remission rates are decreasing and to examine how remission outcomes can be successfully met for these groups (Gaynes et al., 2009; Lopresti et al., 2014). I researched the relationship between inflammatory biomarkers and treatment efficacy for depression. These inflammatory biomarkers respond to the psychosocial stressors associated with

depression, and these both precede and follow diagnosis with major depressive disorder (Miller & Raison, 2016).

Research Design and Rationale

For this study, I employed a quantitative secondary data analysis from an existing dataset from a sponsored experimental, randomized, double-blind, placebo-controlled, and IRB-approved clinical trial (ClinicalTrials.gov Identifier: NCT01098240). I focused on the comparison of an add-on novel pharmacotherapy and placebo in a population diagnosed with depression who demonstrated a previous lack of remission. The independent variables for this study included inflammatory biomarkers: adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα. The dependent variable was the remission outcome, as measured by the MADRS. Mediating variables included age, race, and gender (see Table 1).

In the original study, Fava et al. (2015) failed to achieve efficacy of the novel pharmacotherapy, as compared to the placebo in the augmentation of antidepressant therapy (ADT) in patients with MDD, as measured by the MADRS. The sample selected for their study included a mixed MDD population, and participants were not stratified according to inflammatory biomarker status (Fava et al., 2015). Nicotinic agonists were more efficient compared to acetylcholine at inhibiting the inflammatory signaling and the production of proinflammatory cytokines (Cai, Deitch, & Ulloa, 2010; Jonge & Ulloa, 2007). This nicotinic antiinflammatory pathway might have clinical implications, as treatment with nicotinic agonists could modulate the production of proinflammatory

cytokines from immune cells. Therefore, this study might help to support these conclusions by examining outcomes based on inflammatory biomarkers.

A correlational research design was selected for this study to address the research questions relating to the association or relationships between variables. By using a correlational research design, I could determine the extent of relationship between two or more variables using statistical data. Based on an analysis of relationships using a correlational research design, the researcher can identify whether changes in certain variables are associated with changes in other variables, along with the direction, degree, magnitude, and strength of those associations (Burns & Grove, 2005; McLeod, 2008; Walker, 2005). Correlation does not necessarily imply causation (McLeod, 2008); therefore, no causal relationships were identified in this study.

A correlational quantitative research design was appropriate for this study and was consistent with the research designs needed to advance knowledge in this field. The secondary data set used for this study contained numbers, which were analyzed quantitatively. Additionally, other researchers in this field who have conducted studies relating to inflammatory markers have used similar research designs (Brenner et al., 2014). Empirical research related to the measurement of cytokines was emergent and limited (Brenner et al., 2014); therefore, research designs, such as this, could add to the body of literature relating to these inflammatory biomarkers.

Table 1

Independent, Dependent, and Mediating Variables

Independent Variables	Dependent Variable	Mediating Variables
-adiponectin -C-Reactive Protein (hs-CRP) -leptin -interleukin 1-β (IL1-β) -interleukin 6 (IL6) -tumor necrosis factor-α (TNFα)	-depression remission outcome	-age -race -gender

Methodology

I used existing datasets from a sponsored experimental, randomized, double-blind, placebo-controlled, and IRB-approved clinical trial (ClinicalTrials.gov Identifier: NCT01098240). The data sets were retrieved from the sponsor pharmaceutical company, Pfizer Inc., and transferred to SPSS for analysis. To answer the research questions, an analysis of variance and a linear regression analysis was conducted.

Archival Data

The archival data used for this study were from a clinical study conducted by Pfizer, Inc. between June 2010 and September 2011. The study was an experimental,

randomized, double-blind, placebo-controlled, and IRB-approved clinical trial entitled A Study of the Efficacy and Safety of CP-601,927 Augmentation of Antidepressant Therapy in Major Depression (ClinicalTrials.gov, 2013). The study was identified in a registry housed by ClinicalTrials.gov, which maintained a database of publicly and privately conducted studies in the United States and internationally. The database provided information relating to studies contained in the registry, including the study protocol, the purpose of the study, recruitment status, and the eligibility criteria for participants. The trial selected for this study also included results from the trial as a part of the database registry. To obtain the data set used for this study, I requested permission directly from Pfizer, Inc. To do so, I contacted the Pfizer ClinicalTrials.gov Call Center by phone and via e-mail. A formal written request for the data and permission to use the data for this study were submitted and approved.

Population and Sample

There were 297 participants included in the study. Eligible participants included men and women between the ages of 18 and 65 years. To be included, participants had to have been diagnosed with MDD without psychotic features, with the duration of the current episode of MDD being at least 8 weeks prior to enrollment in the study. Participants were required to receive ongoing treatment using ADT at the time of screening, including escitalopram, citalopram, fluoxetine, paroxetine controlled-release, and sertraline. Otherwise, the participants had to be medically healthy (ClinicalTrials.gov, 2013).

Instrumentation and Operationalization of Constructs

Another instrument used in this study was the MADRS (Montgomery & Asberg, 1979). The MADRS was used by researchers to measure the severity of depressive symptoms in patients. Due to its extensive use, there have been many researchers who validated its use in the assessment of depressive symptoms. For example, Duerte-Guerra et al. (2016) conducted a study to validate the use of the MADRS to assess the depressive symptoms of bariatric surgery candidates. Using a sample of 374 obese patients, Duerte-Guerra et al. compared results from the MADRS to results from the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I). Based on the data of the study, Duerte-Guerra et al. concluded that the MADRS was a reliable and valid assessment tool for depressive symptoms.

Similarly, Kjærgaard, Arfwedson Wang, Waterloo, and Jorde (2014) tested the reliability and validity of several instruments for measuring depressive symptoms, including the MADRS. In their study, healthy participants were interviewed using the MADRS. The SCID-CV was used to diagnose a major depressive episode in the healthy participants and as a result, 6% of the participants were diagnosed as experiencing a MDE. The instruments in question were found to be internally consistent and in alignment with the SCID-CV. Kjærgaard et al. concluded that the MADRS, along with the other instruments, were appropriate screening instruments for identifying MDE in healthy populations.

Data Analysis Plan

Based on the immune-cytokine POD and lack of research on inflammatory biomarkers in mental health, I included the following research questions and associated hypothesis:

RQ1: Is there any relationship between inflammatory biomarkers, including adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H1_o$: There is no relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H1_a$: There is a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

RQ2: Is there any relationship between remission outcomes, as measured by MADRS uniform, for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H2_o$: There are no relationships between uniform remission outcomes for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H2_a$: There is a relationship between uniform remission outcomes for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

RQ3: Is there any relationship between treatment response, as measured by the MADRS, and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H3_o$: There is no relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H3_a$: There is a relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

The data from the clinical trial were transferred to SPSS for analysis. The data were analyzed for any missing data and adjusted accordingly to determine the number of valid data entries that could be included in the research. Missing data were coded as missing in the SPSS worksheet, and participants with missing data were removed from the data set and were not included in the analysis. A one-way ANOVA was conducted to address RQ1 to determine if there was a difference between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who demonstrated a previous lack of remission, as measured by the MADRS. I verified the assumptions of normality, homogeneity of variance, and independence. Data were analyzed using a *p*

value of .05 or below to determine statistical significance. I also noted the effect size of the analysis results.

For RQ2 and RQ3, a multiple linear regression analysis was conducted to determine if there was any relationship between remission outcomes, as measured by MADRS uniform for each inflammatory biomarker. However, for RQ3, the variables were mediated through age, race, or gender (see Table 2). An analysis of the descriptive statistics of the sample was conducted, including measures of central tendency. To test the hypotheses, a multiple linear regression analysis was conducted using SPSS. The output data were analyzed to determine that the data met all assumptions necessary to produce an accurate analysis, namely, independence, homogeneity of variance, and normality. Once the assumptions were met, the results of the linear regression test were analyzed. The analysis was repeated as necessary to identify any mediating variables, as prompted by the significance of the identified relationships (Newsom, 2015).

Table 2

Research Question Analysis

RQ#	Type of Analysis	Descriptive Stats	Hypothesis Testing	Posthoc Analysis
1	One-way ANOVA	Sample size, standard deviation, mean	F statistic	N/A
2	linear regression	Sample size, standard deviation, mean	standardized and unstandardized slope, R^2	N/A
3	linear regression	Sample size, standard deviation, mean	standardized and unstandardized slope, R^2	N/A

Threats to Validity

External Validity

A threat to the external validity of this study was the administration of CP-607,927 and its subsequent dismissal as ineffective. The clinical trial was stopped because the criteria for cessation due to futility were met (ClinicalTrials.gov, 2013). Consequently, it was not known what the influence of the drug had on the variables measured in this study, other than being deemed ineffective as an enhancement to antidepressant therapy. However, because the drug was deemed ineffective, the data were interpreted with that ineffectiveness in mind. CP-607,927 was not considered as an influential factor of the measured variables included in this study.

Internal Validity

The use of secondary data might pose as a threat to the internal validity of the study. Data gathered for a different purpose to answer a different research question could cause a misinterpretation of the variables, the measurement of those variables, and the interpretation of the data (Kimberlin & Winterstein, 2008). However, this threat to validity was mitigated by researching and understanding how the data were collected, the purpose for which these were collected, and the measurement and representation of the variables documented within.

Construct Validity

The construct of depression in this study could be perceived as a threat to the statistical conclusion validity in this study. There were several types of depressive disorders, including major depression, persistent depressive disorder, psychotic

depression, postpartum depression, seasonal affective disorder, and bipolar disorder (NIMH, 2016a). However, the data set used for this study included only participants suffering from MDD. This threat to construct validity was considered when making generalizations about depression and inflammatory biomarkers based on the data contained herein.

Ethical Procedures

The ethical concerns for this study were limited because this study involved the use of an archived secondary data set, containing no personally identifiable information of participants. Prior to conducting the study, permission was obtained from the Walden University Institutional Review Board (IRB; approval number 12-27-16-0280750).

Data received from Pfizer, Inc. were stored on an external electronic storage device and a laptop computer, which only I could access. The laptop and external storage device were kept in a locked safe in the researcher's home, when not being used for the study. Data provided would not contain any identifying information of the participants. Moreover, I would not release or disclose any information that was previously undisclosed and confidential (ClinicalTrials.gov, 2013).

Summary

The problem researched by this study was the relationship between inflammatory biomarkers and treatment efficacy for depression. The purpose of this quantitative secondary data analysis was to determine if there were a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who demonstrated a previous lack of remission and, if so, to what extent. The research

design and methodology were selected to address the study problem, purpose, and related research questions.

This chapter included details relating to the research methodology and design. A quantitative secondary data analysis of an existing dataset from a sponsored experimental, randomized, double-blind, placebo-controlled, and IRB-approved clinical trial was selected to examine the relationships between inflammatory biomarkers and depression treatment efficacy. The data set included data from 297 participants in a clinical trial who suffered from MDD and received antidepressant treatment for their disorder. The data were analyzed using ANOVA and linear regression. This chapter also included addressing the threats to the validity of the study and the ethical procedures taken by the researcher.

The next chapter contains the statistical results of the study. Chapter 4 includes a detailed description and explanation of the data set used. The chapter concludes with an explanation of the results from the statistical analysis.

Chapter 4: Results

Introduction

The purpose of this quantitative study was to determine if there was a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who demonstrated a previous lack of remission. Eligible participants included men and women between the ages of 18 and 65 years who were receiving ongoing antidepressant therapy at the time of screening, including escitalopram, citalopram, fluoxetine, paroxetine controlled-release, and sertraline. The data used for analysis were from a clinical study conducted by Pfizer, Inc. (ClinicalTrials.gov Identifier: NCT01098240) between June 2010 and September 2011. The study was an experimental, randomized, double-blind, placebo-controlled, and IRB-approved clinical trial that provided information relating to studies contained in the registry, including the study protocol, the purpose of the study, recruitment status, and the eligibility criteria for participants.

The outcome/dependent variable measured depression remission, and the independent variables were adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα with three mediating variables: age, race, and gender. A correlation analysis was conducted to address the first research question to determine if a difference existed between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who had demonstrated a previous lack of remission, as measured by the MADRS. For Research Questions 2 and 3, multiple linear regression analyses were conducted to determine if any relationship occurred between remission outcomes, as measured by

MADRS uniform for each inflammatory biomarker in persons diagnosed with depression who had demonstrated a previous lack of remission, as measured by the MADRS. However, for the third research question, the variables were mediated through age, race, or gender.

In this chapter, I present the results of the data analysis methods following the collection and organization of the data, including details on the research questions and hypotheses, a description of the sample used for statistical analysis, and an exploration of the statistical tests used to observe the research questions and hypotheses. The chapter concludes with an overall summary of the findings.

Research Questions and Hypotheses

Based on the immune-cytokine POD and lack of research on inflammatory biomarkers in mental health, the following research questions and associated hypotheses were included:

RQ1: Is there any relationship between inflammatory biomarkers, including adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα and treatment efficacy, in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H1_o$: There is no relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H1_a$: There is a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

RQ2: Is there any relationship between remission outcomes, as measured by MADRS, uniform for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H2_o$: There are no relationships between uniform remission outcomes for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H2_a$: There is a relationship between uniform remission outcomes for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

RQ3: Is there any relationship between treatment response, as measured by the MADRS, and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS?

$H3_o$: There is no relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

$H3_a$: There is a relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

Data Collection

Timeframe for Data Collection

The data were previously collected and readily available from Pfizer Inc. Recruitment of study participants was not applicable because the data were initially collected for other research purposes (i.e., Pfizer-sponsored clinical trial identified as Protocol A3331017 [NCT01098240], entitled A Study of the Efficacy and Safety of CP-601,927 Augmentation of Antidepressant Therapy in Major Depression) by Pfizer Inc. between June 2010 and September 2011. A data access agreement was executed with Pfizer Inc. to acquire the data, which were extrapolated from Pfizer's main internal study database. There were no discrepancies in data collection from the plan presented in Chapter 3.

Demographics

The sample for this study consisted of 107 participants, who were diagnosed with MDD without psychotic features, with the duration of the current episode of MDD being at least 8 weeks prior to enrollment in the study. Participants were required to receive ongoing treatment using ADT at the time of screening, including escitalopram, citalopram, fluoxetine, paroxetine controlled-release, and sertraline. Otherwise, the participants had to be medically healthy. Table 3 shows a summary of demographics for the study participants: female (77.8%, $n = 83$) and 22.4% ($n = 24$) male; and White

(86.0%, *n* = 92), with 13.7% (*n* = 14) Black; and 0.9% (*n* = 1) of mixed race. Average age at baseline was 46.69 years (*SD* = 11.21), and average body mass index was 32.94 (*SD* = 7.94).

Table 3

Summary of Demographics (n = 107)

	N	Percent
Gender		
Male	24	22.4%
Female	83	77.8%
Race		
White	92	86.0%
Black	14	13.1%
Other (Mixed Race)	1	0.9%
	Mean	SD
Age (Years) at Baseline	46.69	11.21
Body Mass Index	32.94	7.94

Study Variables

The independent variables for this study were inflammatory biomarkers: adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα. The dependent variable was the remission outcome, as measured by the MADRS. The change in MADRS total value from baseline was used for all statistical analyses. Mediating variables included age, race, and gender. Table 4 shows a summary of the independent and dependent variables, where adiponectin ranged from 4 to 58 ug/ML, with an average of 16.02 (*SD* = 9.02). Hs-CRP ranged from 0.2 to 8.5 mg/L, with an average of 3.98 (*SD* = 3.03). Leptin ranged from 0.4 to 88 mg/ML, with an average of 26.8 (*SD* = 20.81). Given the large standard deviation (relative to mean) for leptin, the median (IQR) value was 23.0 (9.0 – 38.4). IL1-β ranged

from 1.30 to 3.31, with an average of 1.35 (*SD* = 0.26). IL6 ranged from 0.96 to 40.91, with an average of 2.78 (*SD* = 4.34). TNFα ranged from 0.64 to 9.27, with an average of 2.06 (*SD* = 1.34). The dependent variable, remission outcome measured by change in MADRS from baseline, ranged from -31 to 19, with an average of -8.38 (*SD* = 9.10). To determine if a change in MADRS was clinically meaningful, a one-sample *t*-test was performed to determine if the sample average of -8.38 was significantly different from 10. I found that this sample's remission outcome was clinically meaningful ($t = -20.59$, $p < 0.0001$). Given these results, 49.53% ($n = 53$) of the patients had a remission outcome of -8.38 or lower. In addition, the median (IQR) change in MADRS from baseline was -7.0 (-15.0 – -1.0). Where 49.53% ($n = 53$) of patients were below this median, and 50.47% ($n = 54$) were the same or above this median.

Table 4

Summary of Study Variables

	Mean	Median	SD	Min	Max
Independent Variables					
Adiponectin (ug/ML)	16.02	14.00	9.02	4.00	58.00
hs-CRP (mg/L)	3.98	2.90	3.03	0.20	8.50
Leptin (mg/ML)	26.80	23.00	20.81	0.40	88.00
IL1-β	1.35	1.30	0.26	1.30	3.31
IL6	2.78	1.58	4.34	0.96	40.91
TNFα	2.06	1.89	1.34	0.64	9.27
Dependent Variable					
Remission Outcome (Change in MADRS From Baseline)	-8.38	-7.00	9.10	-31.00	19.00

Generalizability

The patient population selected for research study was considered representative of the broader population, as participants were outpatients, aged 18 to 65 years, who had

a primary current diagnosis of MDD without psychotic features and receiving ongoing ADT with an SSRI without an adequate response to treatment. Inflammatory biomarkers can relate to the heterogeneity within the clinical diagnosis of MDD. Within the defined screening criteria for the research study, there was demonstrated variety in the sample, as participants met screening criteria; however, their inflammatory biomarker levels and depression treatment outcomes differ. There may be a minority of MDD patients within the sample who may be refractory to the treatment, irrespective of inflammatory biomarker measurement. This finding reflected a probable homogeneous subgroup of pathophysiology as related to the general MDD population.

Prediction of efficacy outcomes in patients with varying levels of inflammatory biomarkers at baseline may present limitations in the generalizability of the research study findings to the overall population of those diagnosed with MDD. Conversely, these inflammatory biomarkers informed the relationship between the heterogeneity, pathophysiology of MDD, and the ability of patients to demonstrate efficacy. This might inform the identification of MDD subtypes and advance treatment selection.

Treatment Administration

The treatment was administered, as specified in the original Pfizer-sponsored clinical trial. There were no challenges that prevented planned implementation, as described in Chapter 3. Because this research study was a quantitative secondary data analysis from an existing dataset, no adverse events (AEs) were noted, as this was not applicable. The most common adverse events in the original Pfizer-sponsored clinical trial in participants who received interventional treatment versus placebo were headache

(20.8% *vs* 14.1%) and nausea (14.3% *vs* 14.1%; Fava et al., 2015). Additionally, there was no differentiation between the percentages of participants who permanently discontinued from the original Pfizer-sponsored clinical trial because of AEs in the interventional treatment group (3.9%) versus the placebo group (3.5%), respectively (Fava et al., 2015).

Results

Model Assumptions

To explore the research questions, correlation and multiple linear regression analyses were used. When using these methods, there were several assumptions that must be true for the tests to be valid. Verification of the assumptions of normality, homogeneity of variance, and independence occurred. To test that the data met these assumptions, Shapiro-Wilk tests and an examination of skewness and kurtosis values were observed for normality. Shapiro-Wilk statistic *p*-values > 0.05 (nonsignificant) and skewness/kurtosis values between -3 and 3 were indications of a normal distribution. Additionally, following each regression model, for the assumptions of homogeneity of variance and independence, an observation of a plot of the residuals by fitted values was made. In the results of the Shapiro-Wilk tests and Skewness/Kurtosis observations, I found that there were some study variables that did not fully meet all normality assumptions (see Table 5). For the correlation analysis, both Pearson (parametric) and Spearman (nonparametric) correlations were calculated.

Table 5

Shapiro-Wilk and Skewness/Kurtosis Checks for Normality

	SW Statistic	P-value	Skewness	Kurtosis
Adiponectin	0.83	<0.0001	1.98	5.30
hs-CRP	0.86	<0.0001	0.42	-1.40
Leptin	0.92	<0.0001	0.91	0.35
IL1-β	0.19	<0.0001	6.27	40.93
IL6	0.40	<0.0001	6.78	56.82
TNFα	0.84	<0.0001	1.99	7.43
Remission Outcome	0.98	0.054	-0.21	-0.10

Research Question 1

To explore Research Question 1, Pearson's correlation was used to determine if there was a difference between inflammatory biomarkers (independent variables) and treatment efficacy (dependent variable) in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS. In the results of the correlations (see Table 6), I found that IL6 was the only biomarker that was significantly associated with change in MADRS total score from baseline (Spearman Correlation = 0.24, $p = 0.013$). An increase in IL6 correlated with a mild to moderate increase in remission outcome. All other biomarkers were not statistically significant. The null hypothesis could be rejected for IL6, concluding that there was a relationship between IL6 and treatment efficacy in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

Table 6

Pearson's Correlations with Remission Outcome

	Pearson Correlation	Pearson p-value	Spearman Correlation	Spearman p-value
Adiponectin	-0.11	0.279	-0.01	0.932
hs-CRP	-0.03	0.738	-0.05	0.638
Leptin	0.04	0.665	0.10	0.319
IL1-β	-0.04	0.681	-0.02	0.838
IL6	0.32	0.001	0.24	0.013
TNFα	0.11	0.282	0.11	0.257

Research Question 2

To explore Research Question 2, several simple linear regression analyses were conducted to determine if there was any relationship between remission outcomes, as measured by MADRS uniform for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS. Similar to the correlation analysis, in the results of the regression models (see Table 7), I found that IL6 was the only biomarker that significantly predicted remission outcome ($t = 3.43$, $p < 0.05$). For everyone unit increase in IL6, the change in MADRS from baseline increased by 1.29. In addition, 10.4% of the amount of variability in the outcome can be attributed to IL6. None of the other biomarkers significantly predicted remission outcome. I could reject the null hypothesis for IL6, concluding that there was a relationship between uniform remission outcomes for IL6 in persons diagnosed with depression who demonstrated a previous lack of remission, as measured by the MADRS.

Table 7

Simple Linear Regressions for Each Inflammatory Biomarker by Remission Outcome

	B	SE(B)	β	t	R^2
Adiponectin	-0.11	0.10	-0.11	-1.09	0.011
hs-CRP	-0.01	0.30	0.74	-0.34	0.001
Leptin	0.02	0.04	0.04	0.43	0.002
IL1-β	-1.42	3.46	-0.04	-0.41	0.002
IL6	1.29	0.38	0.32	3.43*	0.104
TNFα	0.72	0.67	0.11	1.08	0.011

Note. $*p < 0.05$

Research Question 3

To explore Research Question 3, several multiple linear regression analyses were conducted to determine if there was any relationship between remission outcomes, as measured by MADRS uniform for each inflammatory biomarker in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS, while checking for mediation of age, race, and gender. Results of each regression (see Tables 8 through 13) showed that age, race, and gender did not mediate any of the relationships between the biomarkers and remission outcome. I could see that the associations between each biomarker and the outcome have not changed when age, race, and gender were added to the model. IL6 remained the only biomarker significantly associated with change in MADRS total score from baseline ($t = 3.50$, $p < 0.05$). These results showed that the null hypothesis failed to be rejected, concluding that there was no relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who demonstrated a previous lack of remission, as measured by the MADRS.

Table 8

Multiple Linear Regressions for Adiponectin by Remission Outcome, Adjusting for Age, Gender, and Race

	B	SE(B)	β	t
Adiponectin	-0.08	0.10	-0.08	-0.81
Age	-0.05	0.08	-0.06	-0.63
Gender (Male)	-3.07	2.26	-0.14	-1.36
Race (Black)	-2.58	2.71	-0.10	-0.95
Race (Other)	-1.27	9.34	-0.01	-0.14

Note. $*p < 0.05$, Model $R^2 = 0.04$

Table 9

Multiple Linear Regressions for hs-CRP by Remission Outcome, Adjusting for Age, Gender, and Race

	B	SE(B)	β	t
hs-CRP	-0.08	0.30	-0.03	-0.27
Age	-0.06	0.08	-0.08	-0.78
Gender (Male)	-3.46	2.21	-0.16	-1.57
Race (Black)	-2.18	2.67	-0.08	-0.82
Race (Other)	-1.69	9.43	-0.02	-0.18

Note. $*p < 0.05$, Model $R^2 = 0.04$

Table 10

Multiple Linear Regressions for Leptin by Remission Outcome, Adjusting for Age, Gender, and Race

	B	SE(B)	β	t
Leptin	0.03	0.04	0.06	0.60
Age	-0.06	0.08	-0.07	-0.70
Gender (Male)	-3.79	2.26	-0.17	-1.68
Race (Black)	-1.89	2.71	-0.07	-0.70
Race (Other)	-0.58	9.45	-0.01	-0.06

Note. $*p < 0.05$, Model $R^2 = 0.04$

Table 11

Multiple Linear Regressions for IL1-B by Remission Outcome, Adjusting for Age, Gender, and Race

	B	SE(B)	β	t
IL1-B	-0.59	3.56	-0.02	-0.17
Age	-0.06	0.08	-0.08	-0.73
Gender (Male)	-3.46	2.22	-0.16	-1.56
Race (Black)	-2.19	2.68	-0.08	-0.82
Race (Other)	-1.38	9.36	-0.01	-0.15

Note. $*p < 0.05$, Model $R^2 = 0.04$

Table 12

Multiple Linear Regressions for IL6 by Remission Outcome, Adjusting for Age, Gender, and Race

	B	SE(B)	β	t
IL6	1.33	0.38	0.33	3.50*
Age	-0.10	0.08	-0.12	-1.23
Gender (Male)	-3.54	2.08	-0.16	-1.70
Race (Black)	-1.27	2.53	-0.05	-0.50
Race (Other)	0.08	8.84	<0.01	0.01

Note. $*p < 0.05$, Model $R^2 = 0.14$

Table 13

Multiple Linear Regressions for TNFα by Remission Outcome, Adjusting for Age, Gender, and Race

	B	SE(B)	β	t
TNFα	0.61	0.68	0.09	0.89
Age	-0.07	0.08	-0.09	-0.84
Gender (Male)	-3.23	2.22	-0.15	-1.46
Race (Black)	-2.09	2.66	-0.08	-0.79
Race (Other)	-1.16	9.33	-0.01	-0.12

Note. $*p < 0.05$, Model $R^2 = 0.04$

Summary

The main purpose of this quantitative study was to determine if there was a relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who demonstrated a previous lack of remission and, if so, to what extent. Results of the analyses showed that IL6 significantly correlated and predicted remission outcome, as measured by change in MADRS total score from baseline. None of the other biomarkers significantly associated with remission outcome. Additionally, there was no relationship between treatment response and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS.

Chapter 5 consists of interpretations of the findings, limitations of this study, recommendations for future studies, and implications. I discuss in more detail what the data mean for the current study, the impact on social change, and how the results can be used for future studies pertaining to the relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who demonstrated a previous lack of remission.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The primary purpose of this quantitative study was to assess the influence of inflammatory biomarkers on treatment efficacy in persons diagnosed with depression, who have previously demonstrated lack of remission. The study was conducted on participants between the ages of 18 to 65 years, who were receiving ADT, including escitalopram, citalopram, fluoxetine, paroxetine controlled-release, and sertraline at the time of screening. Remission outcome was measured in terms of change in the MADRS from baseline. I found that indicated that IL-6, one of the biomarkers investigated in the study, positively related to remission outcome. The other biomarkers studied, namely, adiponectin, hs-CRP, leptin, IL1-β, and TNFα, failed to show the same significant relationship. In addition, I found that age, gender, and race did not act as mediators in the relationship between the biomarkers and remission outcomes.

I used the theoretical backdrop of the immune-cytokine POD (Smith, 1997), primarily because the framework provided a novel medium of exploring the causes of depression by using a cytokine based disease model (Roy & Campbell, 2013; Smith, 1997). Psychosocial stressors associated with depression, preceding or leading to MDD (Miller & Raison, 2016) could activate inflammatory biomarkers. I found that physical processes, such as secretion of cytokines (biomarkers) in patients diagnosed with depression, could have affected the remission outcomes. An increase in IL6 correlated with a mild to moderate increase in remission outcome of patients diagnosed with depression. Perhaps the greatest advantage of using this theoretical framework was that it

helped fill the gaps in understanding the interconnected nature of the physical and mental processes.

Interpretation of the Findings

The following sections of this chapter include interpretation of the study's results in the light of existing literature. Additionally, I discuss the limitations of the research, as well as the implications and impact for social change, and conclude with recommendations for future studies.

Inflammatory Biomarkers and Treatment Efficacy

The first research question stated the following: Is there any relationship between inflammatory biomarkers, including adiponectin, hs-CRP, leptin, IL1-β, IL6, and TNFα and treatment efficacy, in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS? I found that only biomarker IL6 positively correlated to remission outcome. I found that IL6 significantly associated with change in MADRS score from baseline (Pearson correlation= 0.32, p= 0.001), thereby making it a mild to moderate predictor of treatment efficacy in people who were diagnosed with depression but who had previously displayed lack of remission. I also found that the independent variables, consisting of biomarkers adiponectin, hs-CRP, leptin, IL1-β, and TNFα did not show any significant influence on the remission outcomes. However, I noted that the relationship between biomarkers and depression treatment outcomes were correlational, thereby making it hard to illustrate causality.

In spite of the correlational nature of the results, these finding were noteworthy, as these remained consistent with existing research in the field that showed

proinflammatory biomarkers predicted depression. The result that biomarker IL6 was significantly related to treatment efficacy for depression supported earlier researchers who established an association between illnesses with inflammatory conditions and depression (Dowlatia et al., 2010; Sua, 2012; Walker et al., 2014). Furthermore, this finding provided support of the role of IL6 in the etiology of depression. Fonseka, McIntyre, Soczynska, and Kennedy (2015) emphasized how IL6 associated with pathophysiology of MDD, as well as several inflammatory and autoimmune diseases. Fonseka et al. pointed out that pharmacotherapy primarily targeted neurochemical pathways for treating MDD, which revealed low remission rates with high probability of recurrence. Thus, the findings have clinical significance in the diagnosis of MDD and its treatment.

Not all the biomarkers showed a significant relationship to remission outcome, which was also consistent with extant literature (Smith, 1997). Cytokines, which were present in every human body, could be produced with the right stimulation at any given time. However, the secretion of cytokines did not necessarily result in depression. I found that IL6 had a significant correlation with remission outcome, which could help in distinguishing MDD patients from other patient groups demonstrating similar clinical qualities and characteristics. It could also predict the degree to which IL6 influences treatment efficacy for depression. I extended the earlier research (Krishnadas & Cavanagh, 2012) by showing that one of the biomarkers, IL6, could moderately predict remission outcome. Krishnadas and Cavanagh (2012) tried to understand why treatment for depression was effective for some and not others by looking at inflammatory

biomarkers. Maes, Kubera et al. (2012) also postulated that inflammatory biomarkers might be underlying depression.

Maes, Kubera et al. (2012) postulated that the biomarkers might also play a role in how people with depression respond to interventional therapy. Maes, Kubera et al. revealed that the correlational association between biomarker IL6 and remission outcome had connotations for clinicians and therapists who could use the information to evaluate how patients will respond to treatments. Elevated IL6 levels could be used in the diagnosis of depression, which would add value to current diagnostic methods (Lopresti et al., 2014) and treatment options that often culminated to a trial and error process (Chan et al., 2016). Considering the research was conducted on patients diagnosed with depression who had previously shown lack of remission, the results could be used for evaluating why some patients do not respond to certain treatments and therapies. This study provided a more IL6 targeted treatment approach for diagnosing patients with MDD and designing therapies and drugs that might be more effective in treating depression. In addition, it could provide information on more standardized ways of approaching depression, rather than a trial and error approach.

I confirmed the association between IL6 and depression treatment outcomes, which could also contribute to finding novel ways for treating depression. The IL6 biomarker could be used in predicting how patients would react to ADTs. Researchers indicated that the inflammatory biomarkers, such as adiponectin, CRP, leptin, IL1-β, IL6, and TNFα often led to lack of response to therapy and reduction of the effectiveness of antidepressants (English et al., 2010; Raison et al., 2013; Strawbridge et al., 2015).

One of the concerns that arose from lack of proper diagnosis and apposite treatment options was that patients often did not respond to the treatment. Ruland et al. (2016) and Sua (2012) postulated that when patients who were nonresponsive to antidepressants and treatment options were repeatedly exposed to unsuccessful treatments, they often became treatment resistant. High levels of proinflammatory biomarkers at baseline, especially IL6, could help determine lack of response to antidepressants. Under those circumstances, I suggested that a more targeted approach for the population could improve remission results. With the selective inhibition of IL6, the putative effects of antidepressants might be fully used.

Inflammatory Biomarkers and Remission Outcome

The second research question stated the following: Is there any relationship between remission outcomes and inflammatory biomarkers, as measured by MADRS, in persons diagnosed with depression who have demonstrated a previous lack of remission? The results corroborated the findings of the correlational analysis of the previous research question and showed IL6 was the only biomarker that influenced remission outcome (t = 3.43, $p < 0.05$), namely that there was a relationship between the presence of biomarker IL6 and remission outcomes in people diagnosed with depression who previously failed to show proper remission. For every unit increase in IL6, the MADRS score from baseline increased by 1.29. In fact, 10.4% variability in the outcome could be accounted by the presence of IL6. Other biomarkers, including adiponectin, hs-CRP, leptin, IL1-β, and TNFα on remission outcomes, were not statistically associated with remission.

In my study results, I undermined the importance of understanding the roots of depression for improving treatment outcomes. Kessler et al. (2016) pointed to the heterogeneous nature of depression, making it difficult to be conceptualized and treated without understanding its origin. Gaynes et al. (2009) focused on treatment resistant depression and found that remission was a complex process, involving several steps. Gaynes et al. highlighted the need for better diagnosis of the improved regiments of medications. This study highlighted how the presence of certain biomarkers, such as IL6, could modify remission outcomes, thereby providing a probable cause for the differences in how patients responded or failed to respond to medications and therapies.

The study had clinical significance because it could be used in developing individualized treatment options for depression based on their biological composition and ways in which they responded to certain treatments. Redei et al. (2014) underscored the importance of predictive variables in predicting remission outcomes. In spite of the presence of multiple interventional pharmaceutical therapies targeting depression, the remission outcomes following those treatments were unsatisfactory (Hashimoto, 2015; Slavich & Irwin, 2014). The treatment options for depression varied in efficacy. Thus, the identification of the biomarker, namely IL6 as one of the variables that affected remission outcomes, could help further research on improving treatment outcomes by providing more proper assessment and individualized treatments. The results of this study can be used for increasing the chance of successful treatment of patients diagnosed with depression. The relationship between biomarkers and depression might help in identifying individuals at risk for depression.

Responses Mediated by Age, Race, and Gender

The third research question asked the following: Is there any relationship between treatment response, as measured by the MADRS, and inflammatory biomarkers mediated through age, race, or gender in persons diagnosed with depression who have demonstrated a previous lack of remission, as measured by the MADRS? The results from the multiple linear regression analyses conducted supported the null hypothesis, indicating age, gender, and race were not mediating the relationships between the biomarkers and remission outcomes, as measured by MADRS. When age, race, and gender were added to the model, I found that the relationship between each biomarker and remission outcome did not account for any statistical significance, except for IL6, which showed a change in MADRS total score from the baseline ($t = 3.50$, $p < 0.05$). I stopped reviewing here. Please go through the rest of your chapter and look for the patterns I pointed out to you. I will now review your references.

The study corroborated Wolitzky-Taylor et al. (2012), in which the researchers found that factors, such as race, gender, age, comorbidity, or severity of the disorder, did not predict treatment outcomes in their investigation of the effectiveness of cognitive behavioral therapy (CBT) in comparison to acceptance and commitment therapy (ACT) for treating anxiety disorders. Hauser et al. (2002) investigated whether interferon (IFN) induced MDD could be effectively treated with antidepressants. Hauser et al. also found that history of MDD, substance use, age, or gender did not mediate treatment outcome.

Contrary to the findings of the current study, some studies found age as an important mediator in the relationship between biomarkers and treatment outcomes for

depression (Allison et al., 2014; Luby, 2013; Mills et al., 2013). It must be noted that this study only focused on individuals ranging in age between 18 to 65 years. The other researchers that found age to mediate the association of biomarkers to treatment outcomes often focused on age groups beyond the scope of this study (Allison et al., 2014; Luby, 2013; Mills et al., 2013). Luby (2013) found that children as young as 3 years of age showed signs of depression and discovered that detection and early intervention was essential to ensure long-term effects for these young children. Allison et al. (2014) also pointed to the importance of early detection and proper treatment of depression in children to prevent further deterioration of condition. In addition, Mills et al. (2013) found that adolescents diagnosed with depression illustrated certain age-specific immune and inflammatory system characteristics. Mills et al. had also found that factors, such as neurodevelopment, hormones, stress, and trauma, affected the role played by cytokines in adolescents with depression.

I also did not find race as a mediating factor in the relationship between biomarkers and remission outcomes in patients diagnosed with depression, who had illustrated lack of remission. Hauser et al. (2002) found that significantly lower number of African Americans had depression. Similar to the other mediating variables of age and race, the current results did not find gender to mediate the connection between biomarkers and depression remission outcomes.

Existing research, focusing on gender as a mediating factor in treatment outcome, were inconclusive. Hauser et al. (2002) and Wolitzky-Taylor et al. (2012) did not find that comorbidity, race, gender, age, or severity of the disorder was predictive of treatment

outcomes. However, Miller and Raison (2016) found that depression in women increased significantly when compared to men, which became even more pronounced during the reproductive years.

Miller and Raison (2016) have shown also shown gender as a mediating factor affecting the relationship between biomarkers and treatment outcomes. Studies have revealed women were more prone to the effects of inflammation on behavior, resulting in more significant symptoms of depression (Miller & Raison, 2016). Inflammation might have negative effects on fertility and lactation, both of which could partially explain the higher incidence of depression among women compared to among men (Miller & Raison, 2016). Being prone to depressive symptoms caused by inflammation, women might also have been provided with more protection to fight infection and heal wounds, as well as avoiding illness. The lack of evidence of age, race, and gender, as influencing the association between treatment outcomes and biomarkers, warranted further research.

This quantitative study determined, to some extent, the relationship between inflammatory biomarkers and treatment efficacy in persons diagnosed with depression who previously demonstrated lack of remission. I showed that only biomarker IL-6 correlated to treatment efficacy and that age, race, and gender did not mediate the aforementioned correlation.

Limitations

The scope of this research study remained limited to the variables and associated data from a clinical study conducted by Pfizer, Inc. between June 2010 and September 2011, on outpatients between the ages of 18 and 65 years. I considered correlations of the

specific biomarkers, namely, adiponectin, C-reactive protein (hs-CRP), leptin, interleukin 1-β (IL1-β), interleukin 6 (IL6), and tumor necrosis factor-α (TNFα), with depression treatment efficacy and depression remission outcomes, as moderated by the demographic factors of age, race, and gender. The results from this secondary data did not necessarily carry over to the larger patient-population suffering from depression. There were no discrepancies in data collection from the plan, as it was restricted to secondary data from the original study conducted by Pfizer, Inc.

Second, I assumed that focusing only on the six specific biomarkers would prove sufficient for the purposes of the study. However, other inflammatory biomarkers might have related to treatment efficacy and remission outcomes, in addition to the ones that were part of the study. Third, I applied multiple linear regression analysis, which tested for association but not causality. Additional research was needed to help to establish a causal relationship. Fourth, I noted that cytokines were not only present in all humans, but these could also be produced under the right stimulation. I suggested that the cytokines, considered in this research (INFα, TNF, IN1, etc.), have the potential to cause depression in most but not all subjects. I had to remain cautious about generalizing the findings to include all cytokines.

Fifth, I did not consider other factors that affected remission. For instance, researchers indicated that the patients' perspective influenced the state of remission (Zimmerman et al., 2012). Thus, remission might be a subjective state. Sixth, the conceptual framework of immune-cytokine POD (Smith, 1997) was a newer method of looking at the role biomarkers played in depression by the presence in the brain,

endocrine system, and immune system. As such, the validity and reliability of this framework might be questioned (Brenner et al., 2014).

Seventh, there were other theoretical and conceptual models identified in the study, including the affective response model (Zhang & An, 2013) and the social signal transduction theory of depression (Slavich & Irwin, 2014). However, given that the study depended on secondary data, the alternative conceptual models could not be evaluated. Finally, overwhelming majority of the sample consisted of females (77.8%) and White individuals (86%). The findings might not be generalizable to larger population. Further research should include a more representative sample.

Recommendations

I defended the immune-cytokine MOD theory by showing how cytokines (the biomarkers in the study) could predict treatment efficacy and outcome for depression. I showed that biomarker IL-6 significantly correlated to remission outcome, whereas the other biomarkers, such as adiponectin, hs-CRP, leptin, IL1-β, and TNFα, were not correlated. Future researchers could focus on causation and provide concrete evidence of the relationship between biomarkers and remission outcomes.

Future researchers could also be conducted to advance the theory by probing deeper into the physical and mental processes that influence the development and remission depression. More studies are needed to support the validity of the relatively new alternative approach of studying the effects of cytokines on depression treatment outcomes through the immune-cytokine MOD theory. Further, researchers could also identify the degree to which specific biomarkers that influence remission outcomes.

Longitudinal studies spanning across several years might also provide more accurate data about the lengthy process of remission. Future researchers investigating the influence of biomarkers on antidepressants might yield better results in pharmacotherapy. Miller et al. (2003) found that depression symptoms and activation of inflammatory response could potentially modify the remission outcome for depression treatments. Better drug development research could pave the way for improving treatment efficacy and outcomes.

In spite of the widespread prevalence of depression in patients, irrespective of their age, gender, or race, treatment options lagged behind the demand for treatment. The available treatment options often resulted in a trial and error process due to the lack of proper research on treatment efficacy. The depression treatment outcomes failed to achieve the desired remission goals. The above scenario warranted a better look at empirical research and findings to optimize interventional pharmaceutical therapies for patients. Researchers could use the data from the current study, as well as similar studies, to inform clinicians and therapists to provide the best treatments and medications.

Future researchers should also research specific age groups and assess the implications of depression. There was a scarcity of research on how depression affected young children and the treatment options that could ensure remission. Depression in elderly people was misdiagnosed, leading patients receiving incorrect treatment (Karlsson et al., 2016). Future researchers should educate people about the heterogeneity of depression and how it yielded adverse effects in terms of symptoms, decreased productivity, increased morbidity, and suicidal tendencies (Wray et al., 2012). Future

researchers should design studies concentrating on the adverse effects of depression and find the underlying factors. Reliable and valid data could help remove some of the stigma associated with depression and usher in social change.

Implications

The results of the study have important implications for positive social change. Depression proved a heavy burden on individuals, families, and society. Wray et al. (2012) emphasized how depression had adverse effects on individuals in terms symptomatology, decreased productivity, and increased sense of morbidity. The stigmas associated depression often made it harder for patients to seek professional help (Czyz et al., 2013). Depression was responsible for the high suicide rates (Wray et al., 2012). Billions of dollars were spent annually in identifying and treating depression (Greenberg et al., 1993). In spite of the proliferation of depressive disorders in people, the efficacies of available treatments remained limited (Gaynes et al., 2009).

The results from the current study could help developing early intervention strategies for decreasing incidence of suicides. Researchers showed that MDD patients with suicide ideation display high levels of the IL6 and CRP (Fonseka et al., 2015). IL6 has been the most dominant cytokine that has been linked with suicidal ideation and in fatal as well as nonfatal suicide cases (Mormile, 2016). This study could benefit intervention therapists by indicating the role of IL6 in inflammation and its subsequent influence on the pathophysiology of MDD and showing that treatment targeting IL-6 could yield alleviation from suicidal tendencies.

The findings also have significant implications for improving remission outcomes by identifying high-risk individuals prior to any depressive episode. Bredt et al. (2015) emphasized the importance of distinguishing at-risk individuals and factors that triggered the expression of the disease might help in incorporating avoidance practices that would delay or even stem the disease from occurring. Some of the ways that these could be achieved was by screening for IL6, blood sampling, to ascertain the association between inflammatory cytokines and behavioral symptoms (Felger et al., 2013). The findings would help identify individuals, who might fail to respond to treatment due to presence of higher levels of IL6.

I, by using a cytokine based approach for finding a resolution for depression related issues, provided an enhanced platform for identifying and stratifying patients with respect to bio-signatures and phenotypic traits. This approach was more biology based rather than symptom based categorization, as symptom based grouping could lead to overlapping and clubbing of patients with diverse illnesses but similar behavioral symptoms.

I, along with other extant research, could provide information on ways to detect and treat depression to improve chances of remission. Researchers showed that depression in young children, if it remains untreated, could have severe consequences later in life (Luby, 2013). Researchers could use the research findings to analyze the underlying causes of depression in individuals, as well as for predicting treatment responses. The findings could be used by clinicians to tailor treatment to address

depression in a variety of scenarios, such as preschool children, suicidal tendencies in adolescent depression victims, or elderly people who were misdiagnosed.

Miller and Raison (2016) showed women were more prone to the effects of inflammation on behavior, resulting in more significant symptoms of depression, and the symptoms became more pronounced during their reproductive years. Miller and Raison also showed that inflammation might have negative effects on fertility and lactation, thereby increasing the chances of depression in women (Miller & Raison, 2016).

The findings of the study have great implications in the areas of theory, research, and practice. I advanced human models of depression by focusing on biological systems that affect the etiology of depression. Bredt et al. (2015) demonstrated how experimental human models, associated with mood disorders, could use biological factors of depression to design intervention that simulate biological conditions to trigger depression related behaviors and assess the impact. I also provided valuable insight into the biological factors that influenced depression by revealing that production of increased levels of IL6 could affect remission outcomes.

Another important contribution of this study to the field was that biomarker levels could be used to select appropriate therapeutic treatments. Given that the pathogenesis of most of mood disorders remained unclear, it was hard to deliver treatment options tailored to individual requirements (Bredt et al., 2015). I provided data that counterbalanced those challenges by showing how biomarker levels could help identify interventional therapies that would demonstrate high efficacy for treatment resistant patients.

I analyzed the causes of depression from a relatively new perspective by looking into the relationship between inflammatory biomarkers and its effects on remission outcomes. It could also help clinicians and pharmaco-therapists to explore alternative methods of treatments for optimizing outcomes. Proper diagnosis could curtail the serious repercussions depression has on individuals, by being able to identify upfront those, who are more likely to respond to treatment and those who might not. Individuals, who were at risk and would not respond to the treatment, could then follow other therapies that suited their specific needs in terms of their biological compositions.

Researchers showed that the presence of IL6 might affect clinical response to novel therapies (Martin, Tansey, Schalkwyk, & Powell, 2015). Biomarker IL6 has the capability of inhibiting the production of serotonin in raphe neurons, which could explain why high levels of IL6 could influence efficacy of outcomes in therapies that are still under development (Martin et al., 2014).

Utilizing the immune-cytokine POD theory (Smith, 1997), I provided a new approach to understanding depression with respect to inflammatory biomarkers. I found results that supported the immune-cytokine MOD theory by illustrating the correlation of cytokines (i.e., biomarkers in IL-6, in the study) to treatment efficacy and outcome for patients diagnosed with depression who have shown lack of remission. Analyzing the results with respect to the tenets of the theory has shown how physical and mental processes could influence treatment outcomes for depression.

I identified specific biomarkers that were both correlated (IL-6) and not correlated (adiponectin, hs-CRP, leptin, IL1-β, and TNFα) to treatment efficacy and outcomes for

patients diagnosed with depression. This finding might provide a more tailored list of variables that future researchers might study. Future researchers might be able to identify other biomarkers that affect remission outcomes.

Through the literature review, I also revealed how other factors could affect remission outcome for depression (Zimmerman et al., 2012). Zimmerman et al. (2012) found that remission could be subjective state that was contingent upon the patients' perceptions. Thus, I found it necessary to view the findings of the current research, as one possible way of analyzing treatment outcome among several others. I showed that age, gender, and race did not act as mediators in the relationship between biomarkers and remission outcome in patients diagnosed with depression. This finding could aid researchers in delving deeper and finding the true implications, if any, of those factors in the treatment of depression. I extended earlier research (Krishnadas & Cavanagh, 2012) by showing that one of the biomarkers, IL-6, could moderately predict remission outcome. The results could provide valuable insights into modifying pharmacotherapies for specific subpopulations suffering from depression.

Conclusion

Depression is one of the most significant diseases afflicting individuals, leading to considerable increase in healthcare and disability costs. It is *heterogeneous*—meaning, its symptoms and effects vary on a case-by-case basis. As such, diagnosis of depression often depends on unreliable and inconsistent symptoms. Current pharmaceutical therapies often lag behind in achieving the desired level of recovery in patients. Even though there are resources that address the effect of inflammatory biomarkers on depression, more

questions need to be answered as to how these affect treatment efficacy. Researchers are also unsure about how age, race, and sex mediate the influence of inflammatory biomarkers on treatment efficacy and remission outcomes. While the effects of inflammatory biomarkers are typically manifested in a person's adolescent years, studies regarding the severity of such impact are rare.

Due to the heterogeneity in the types of depression that inflicts patients, some healthcare providers resort to multiple avenues of treatment simultaneously. Such measures lead to a prolonged and chaotic treatment regime on the patient, with no certain solution sight. The current research was conducted in the backdrop of these shortcomings to achieve a better understanding of the following three questions:

1. How inflammatory biomarkers is related to TE.
2. If the RO are the same irrespective of the type of IB
3. If the relation between IB and TE is mediated by age, race and gender.

Using a combination of correlation analysis and multiple linear regression, I found partial support for the three hypotheses of this study. The outcome/dependent variable measured depression remission, while the independent variables included adiponectin, hs-CRP, IL1-β, IL6, and TNFα. The three mediating variables included age, race, and gender. One of the advantages of the research methods used in the study was that I focused only on recent research, mostly restricted to those published in the last 4 years. This focus not only made the study up-to-date, but also more reliable in understanding where research stands today and the future directions needed for advancing the knowledge.

As to the first question, I showed that IL6 was the only biomarker that was significantly associated with change in MADRS total score from baseline. An increase in IL6 was correlated with a mild to moderate increase in remission outcome. The relationships of remission outcome and all other biomarkers were not statistically significant. I also found that IL6 was the only biomarker that considerably predicted remission outcome, along the lines of the previous outcome. For every one unit increase in IL6, the change in MADRS from baseline increased by 1.29. IL6 was still the only biomarker significantly associated with change in MADRS total score from baseline. Finally, I observed that demographic variables (e.g., age, race, and gender) did not mediate any of the relationships between the biomarkers and remission outcome. The findings appeared robust, as IL6 turned out to be the only inflammatory biomarker significantly associated with change in MADRS score from baseline. Future researchers must use caution in generalizing the effects of the study because of the nature of heterogeneity in the depression symptoms.

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