Depression: inflammation as a cause, marker and target for adequate treatment

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2012
Acknowledgements

Thank you to Angele McGrady, Ph.D., University of Toledo Department of Psychiatry, for your guidance and support throughout this project. Also, thank you to The University of Toledo Physician Assistant faculty for your continued encouragement and assistance.
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Chapter 1: Introduction

Depression is a common disease that affects a vast amount of people. It can occur in patients with comorbid illnesses, such as heart disease, lung disease, diabetes, and cancer. Patients with combined mood and physical problems have worse outcomes overall, compared to those without depression (Miller, Maletic, & Raison, 2009). Patients continue being diagnosed and treated with depression; however, some patients are living with symptoms of depression, because they are misdiagnosed or under-treated. New research is showing that inflammation may be related to depression, which opens a door to new diagnostic measures and treatment options for depression.

There has been recent research that shows that inflammation is related to depression, and medications that reduce inflammation may have a role in the treatment of depression. Acute phase proteins have been shown to be elevated in patients with major depressive disorder. The acute phase proteins are markers in the blood that can be used to support the diagnosis of depression. These markers are a great adjunct to the diagnosis of depression, which is based on the Diagnostic and Statistical Manual of Mental Disorders. In addition, anti-inflammatory medications have shown to be effective as additional treatment options, along with traditional management of the illness, for patients with depression.
Chapter 2: Methods

Search Terms Included:

Depression, C-reactive protein/CRP, Depression and C-reactive protein, Inflammation and depression, Major depression and C-reactive protein, Acute phase proteins and depression, Biomarkers for depression, Treatment of depression, Immune activation in depression, Anti-inflammatory drugs for depression, Psychoneuroimmunology

Databases:


Inclusion and Exclusion Criteria for Articles:

Inclusion and exclusion criteria were used in order to generate the most accurate information and ensure quality data was included. All articles were in English and based on populations in the United States, unless there was not enough information on this population; then, other populations most similar to the US were considered first. Background information was compiled from online medical sources, such as access medicine and PubMed first, since these are the most up to date reference bases. In addition, textbooks were used if more information was needed. Clinical review articles as well as peer reviewed journal articles made up the bulk of the supporting references. Primarily those studies using double blind randomized controlled trials were sought for supporting evidence. If these studies were scarce, other randomized trials were
reviewed for accuracy and validity, and those articles demonstrating both of these qualities were included. Exclusion criteria were used to help eliminate false or inaccurate data. Any articles funded by companies or corporations were excluded if they were determined to be written for financial gain by the author. In addition, studies that had too small of a sample size, insufficient statistics, or biased populations were not included. It was important that articles were accurate and generalizable to a larger population.
Chapter 3: Discussion

Depression is a major disorder that affects a wide range of people, and it predicts functional disability and mortality in patients with comorbid physical illnesses. A large amount of healthcare dollars, estimated at 83 billion dollars per year, is spent on depression. According to the Centers for Disease Control and Prevention, as many as 17 million Americans suffer from this condition each year. Studies show that depression causes disability along with social and role impairments, more often than other chronic diseases, such as diabetes, arthritis, hypertension, and coronary artery disease (Cole, Christensen, Cole, M., Cohen, & Feldman, 2008). Yet, many patients who have depression remain undiagnosed or under-treated. Patients who are diagnosed and adequately treated for depression function better overall, compared to those who are not treated or who are under-treated. So it is important that patients suffering with depression get diagnosed correctly and treated effectively, in order to be able to function better in their daily living.

There are many different types of depression with different symptoms and durations. Major depression is defined by the patient exhibiting five or more of the following symptoms: depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide. Also, at least one symptom is either depressed mood or loss of interest or pleasure, and the symptoms must be present most of the day nearly every day for a minimum of two consecutive weeks. Dysthymic disorder is marked by depressed mood for at least two years with depression
present most of the day, for more days than not, and accompanied by two or more of
the following: decreased or increased appetite, insomnia or hypersomnia, low energy,
poor self-esteem, poor concentration, and hopelessness. Minor depression consists of
the manifestation of several of the nine symptoms of major depression, but fewer than
with major depression and/or for a shorter duration; also, patients do not necessarily
exhibit the symptom chronicity of those with dysthymic disorder. Melancholia is a
severe form of major depression which includes lack of mood reactivity to pleasurable
stimuli, loss of pleasure in nearly all activities, worse moods in the morning, early
morning awakenings, psychomotor retardation or agitation, significant weight loss,
and/or inappropriate guilt. Also, patients with melancholia can experience psychosis. In
addition, depression is seen in patients with bipolar I and II disorders, but these patients
exhibit mania or hypomania along with the depressive symptoms (American Psychiatric
Association [APA], 2000). The focus of this paper is on major depressive disorder.

The lifetime prevalence of major depression is 7-12% in the male population and
20-25% in the female population. The usual onset begins in patients younger than 40.
In addition, recent studies show that the “baby boomer” generation is being diagnosed
with major depressive episodes more than any other generation. However, elderly
patients, over the age of 65, have the highest incidence of misdiagnosis of depression,
due to cognitive impairment (Cole, Christensen, Cole, M., Cohen, & Feldman, 2008).
So, depression affects a wide range of people, and diagnosing and adequately treating
it are a necessity to improve patients’ quality of life. According to Miller, Maletic, and
Raison (2009) major depression is a primary cause of disability worldwide, and
sometimes it can even be fatal. So the effects of this disorder are devastating to the
patient and the patient’s family and friends. Since depression creates symptoms at the psychological, behavioral, and physiological levels, it is a complex disease that manifests itself in a variety of ways that are restricting to the patient (Akhondzadeh et al., 2009).

The current standard for diagnosing depression is based on the *Diagnostic and Statistical Manual of Mental Disorders* criteria (APA, 2000). It involves health care providers recognizing the presenting symptoms as possibly being related to depression, using a screening tool, and asking pertinent questions. So at this time, the diagnosis has room for subjectivity and lacks a true objectively diagnostic measurement. Depression tends to be a gradual and progressive disease, so patients may not know how severely their life is being affected or realize they are experiencing abnormal symptoms, such as fatigue, decreased appetite, or psychomotor retardation. In addition, other comorbid conditions, such as cancer, Parkinson disease, and hypothyroidism can cause similar symptoms; therefore, patients may be treated for these conditions and have their depression overlooked (Cole, Christensen, Cole, M., Cohen, & Feldman, 2008). So many times patients are undiagnosed or underdiagnosed, which leads to poorer quality of health, emotionally as well as physically. It would be helpful if there was a diagnostic marker to indicate the presence of depression, so this disorder could be detected easier, and then patients could be adequately treated for their depression, which is ultimately the root cause of their physical symptoms.

Numerous screening tools are available for clinicians to use in order to diagnose depression in a patient. One of the most widely used scales is the Beck Depression Inventory (BDI, BDI-II), which is a self-reporting questionnaire. The test is made up of
questions relating to symptoms of depression such as hopelessness, irritability; cognitions such as guilt or feelings of being punished; and physical symptoms such as fatigue, weight loss, and lack of interest in sex. The severity of depression can be assessed based on the number of positive answers the patient marks, 0-4 positives correlates to none or minimal depression, 5-7 equals mild depression, 8-15 is moderate depression, and >15 is severe depression (Beck, Steer, & Brown, 1996). The 9-Question Depression Module of the Patient Health Questionnaire (PHQ-9) is another tool used by primary care clinicians to diagnose depression and monitor the treatment of it. It is filled out by the patient and assesses for symptoms and functional impairment related to depression, and it develops a severity score depending on how severely the patient is affected by their illness. Patients scoring 5-9 positives have mild depression, 10-14 moderate depression, 15-19 moderately severe depression, and 20-27 severe depression (Kroenke, Spitzer, & Williams, 2001). The Center for Epidemiological Studies Depression (CES-D) Scale is a self-test that measures depressive feelings and behaviors over the previous week (Radloff, 1977).

In addition, there are tests that require more involvement by the clinician. The Diagnostic Interview Schedule (DIS) is a self-reporting test that inquires about more than thirty mental disorders. It has depression and mania subsections that allow a trained interviewer to assign a DSM-III-R diagnosis; this assessment tool has been shown to be a valid instrument for the diagnosis of major depression in epidemiological studies (Robins, Helzer, Croughan, & Ratcliff, 1981). The Hamilton Depression Scale (HDS or HAMD) is another way of evaluating the severity of depressive symptoms in individuals. It is used in conjunction with clinical interviews with depressed patients.
The HDS is administered by an interviewer and rated by them, so there is some subjectivity when it comes to interpretation and scoring. Also, self-esteem and self-deprecation are not assessed with this test; however, questions about anxiety are included (Hamilton, 1960). These are just a few of the evaluations used to help clinicians diagnose depression. They are subjectively based on the patient and the clinician; however, these assessments would be made stronger by a true objective measure to help aide in the diagnosis of depression.

**Inflammation Related to Depression**

Recent studies have shown that inflammation appears to play a role in depression. The body’s inflammatory response involves three major stages: first, capillaries dilate and increase blood flow; second, plasma proteins exit the bloodstream; and third, leukocytes exit the vasculature system and accumulate at sites of injury. There are many acute phase proteins that are produced and elevated in the blood when this activation and inflammation occurs; interleukin-6 and C-reactive protein are two of these, which are the focus of this paper. Interleukin-6 (IL-6) is a cytokine that acts as both pro-inflammatory and anti-inflammatory, and it is secreted by T cells and macrophages to stimulate immune response. C-reactive protein (CRP) is a protein produced by the liver and found in the blood that appears after an injury, infection, or inflammation and usually decreases or disappears when the injury heals or the infection or inflammation goes away. Inflammation is a key component of the immune system that seems to play a part physiologically in depressed patients (Kishiyama, 2010). Both, IL-6 and CRP can easily be measured from a blood sample, so diagnostic tests for these markers could be a possibility for objectively diagnosing depression in patients.
A study by Michael Maes et al. in 1995 investigated the plasma levels of acute phase proteins and their receptors during the acute phase of major depression. The study showed that patients with major depression irrespective of whether or not the patients also exhibited melancholia had higher plasma levels of IL-6 and other proteins as well as receptors for those proteins compared to non-depressed subjects. The results support the idea that IL-6 hyperproduction occurs in patients with major depression. Also, Maes et al. (1995) stated that IL-6 may play a role in the pathogenesis of major depression by altering immune responses that ultimately increase prostaglandin secretion; however, the study showed that the proteins are produced independently of the disease severity. So the immune system is activated in patients with major depression, but the amount of acute phase proteins, such as IL-6, does not correlate with the severity of depression.

Yekta Dowlati et al. (2010) performed a meta-analysis that was designed to determine whether concentrations of specific cytokines related to the immune system differed between patients meeting criteria of major depression and healthy control subjects. Four hundred and ninety-two depressed and 400 non-depressed subjects, in which specific ages of participants were not given, were studied by 16 different analyses, and the results showed that depressed individuals had significantly higher concentrations of IL-6. The meta-analysis went on to show that IL-6 and other acute phase proteins are secreted into the bloodstream in response to immunological insults. IL-6 is secreted by macrophages and monocytes when the immune system is activated and causes differentiation and proliferation of B cells, which are part of the adaptive immune system. So this data supports the hypothesis that the immune system is
activated in depressed patients. Also, the meta-analysis describes how proinflammatory cytokines affect mood by regulating hippocampal neurogenesis. There is a reduction in hippocampal volume seen in major depression, which may be due to a decrease in neurogenesis. Higher levels of IL-6 have been associated with reduced hippocampal gray matter volume. So the theory is that patients with major depressive symptoms have higher levels of IL-6 which causes the hippocampal volume to decrease. Some treatments of depression are already targeted towards the diminished volume; selective-serotonin reuptake inhibitors upregulate brain-derived neurotropic factor (BDNF) in the hippocampus, which is designed to promote the proliferation and survival of neural progenitor cells in this area. So, IL-6 may be a good diagnostic marker to support the diagnosis of major depression and it may be linked to the severity of depression.

Miller, Maletic, and Raison (2009) discuss how cytokines act centrally in the brain and can cause depressive symptoms. Cytokines interact with the different pathophysiological processes of depression; including neurotransmitter metabolism, neuroendocrine function, and neural plasticity. It is unclear as to whether peripherally located cytokines enter the CNS or if inflammatory pathways in the CNS itself cause the changes. Research has shown that peripheral cytokines can communicate with the brain and magnify central inflammatory responses. Cytokines in the brain are able to impact the synthesis, release, and reuptake of mood-relevant neurotransmitters. So regardless of whether inflammation and cytokines directly act in the CNS or access the CNS from the periphery, it is clear that they cause changes in the brain that are linked to depression.
Cytokines have been shown to stimulate the hypothalamic and pituitary cells to increase the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. All three of these were increased in patients with depression (Miller, Maletic, & Raison, 2009). Also, there is evidence that depressed patients exhibit dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Dowlati et al., 2010). A hallmark of major depression is impaired negative feedback regulation of the HPA axis. In a healthy individual, increased concentrations of glucocorticoids or corticosteroids inhibit the release of ACTH, which decreases cortisol levels. This is the result of normal negative feedback regulation, which in depressed patients does not work correctly (Schimmer, 2011). When depressed individuals received dexamethasone, a glucocorticoid steroid, cortisol concentration increased instead of decreasing. Depressed patients have a decreased response or resistance to glucocorticoids because the negative feedback loop does not work correctly. It is believed that the glucocorticoid receptor is altered. Cytokines and inflammatory signaling molecules have been shown to inhibit glucocorticoid receptors. Also, cytokines decrease the number of active glucocorticoid receptors and increase the number of inactive glucocorticoid receptors (Miller, Maletic, & Raison, 2009). This creates the decreased response to dexamethasone in depressed patients, and it accounts for the dysregulation of the negative feedback loop of the HPA axis. This evidence shows that there is a link between inflammation and cytokine production in depressed patients.

A new diagnostic marker may be available to help support the clinical diagnosis of depression in patients meeting the DSM criteria, in conjunction with the previously
listed evaluations. Danner, Stanislav, Abramson, and Vaccarino (2003) performed a study measuring C-reactive protein (CRP) and its relationship to major depression or major depressive episodes. The population of the study included 6,100 U.S. adults aged 17 to 39; the depression and mania subsections of the Diagnostic Interview Schedule (DIS) were used to determine the diagnosis of major depression. Younger aged adults were used in this study in order to decrease the prevalence of clinical and subclinical diseases. Pregnant women, individuals with diseases known to affect CRP levels, individuals with cardiovascular disease and/or diabetes mellitus, individuals with chronic inflammatory disorders, and individuals with bipolar disorder were excluded. The results showed that men with a history of major depressive episode were approximately twice as likely to have an elevated CRP compared to men without a history of this diagnosis; however, this study did not show an association of elevated CRP levels in women diagnosed with major depressive episodes based on the DIS criteria. In addition, men who had a major depressive episode within the past month or 1-6 months prior to this testing had elevated CRP levels. Men who had a major depressive episode greater than 6 months ago had CRP levels that were close to the same value as men who had never had a diagnosis of major depressive episode (Danner et al, 2003).

Howren, Lamkin, and Suls (2009) performed a meta-analysis to study the associations of depression with CRP, IL-6, and IL-1. There are few studies on the relationship of IL-1 and depression, and the relationship between these two entities is not discussed in this paper. Overall, the results showed that analysis of 49 studies concluded there was a positive relationship of CRP with depression. In addition the
meta-analysis analyzed the generalizability of this finding based on characteristics that can affect CRP levels and/or causes of major depression. This analysis showed that variation in the average age of the patients studied did not change the results of the association of elevated CRP with depression. There were not very many studies that separated the results according to gender. However, of those studies that did separate men and women, there was a significant association of CRP with depression in men and a nonsignificant relationship in women. One potential reason why there is not a significant relationship seen in women when they are partitioned out in the studies is because inflammatory responses fluctuate in women with their menstrual cycles.

Depressed patients in a clinical setting had a moderate association with elevated CRP levels, and a smaller association of elevated CRP was seen in depressed patients in community-based populations. When it came to assessing for depression, there was a moderate association of CRP with depressed patients diagnosed using a clinical interview and a smaller association with patients using a self-report measure, such as the BDI, CES-D, or PHQ-9. There was still a significant association of CRP with depression seen in studies that adjusted for body mass index (BMI), but the association was smaller than those studies that did not adjust for BMI. The association between increased BMI and inflammation could explain the increased association of CRP and depression in studies not adjusting for this (Howren, Lamkin, & Suls, 2009).

The meta-analysis of 61 studies revealed that IL-6 was also positively associated with depression. The relationship between IL-6 and depression became smaller as the average age of the people studied increased; however, average ages were not listed. Again, there were not very many studies that separated men from women. In those
studies that did, the opposite of what was seen in CRP was observed among men and women. Men did not have a significant relationship between IL-6 and depression; however, women proved to have a significant relationship between elevated IL-6 and depression. Studies including depressed patients in a clinical setting had a large effect size when showing the relationship among IL-6 and depression. Similarly, populations in the community were shown to have a positive association among the two factors. There was a moderate association seen in studies using clinical interviews to assess for depression, and a much smaller association was seen among studies using self-reporting diagnostic tools. Also, the association between IL-6 and depression decreased when studies adjusted for body mass indexes (Howren, Lamkin, & Suls, 2009).

There is a clear link of elevated CRP and IL-6 in patients who are shown to be depressed when using different depression scales as diagnostic tools. Studies support a higher incidence of significant CRP elevation in depressed males, and a higher incidence of significant IL-6 elevation in depressed women. So these serum markers are able to be used as supportive objective measures to help diagnose depression in adult patients. Now that it is clear inflammation plays a role in depression with acute phase protein activation and increased levels of CRP and IL-6, how can we use this towards the treatment of depression and better functionality in patients diagnosed with depression?
Treatment of Depression; Anti-Inflammatory Augmentation

Since inflammation is a key component of depression, anti-inflammatory medications used in combination with the standard treatment of depression will help treat depressed patients more adequately. Current treatment options for depression include cognitive-behavioral therapy, psychodynamic therapy, and medications. Cognitive-behavioral therapy and psychodynamic therapy aim at determining the cause of the patient’s depression, making the patient aware of the cause, and changing their behaviors; whereas, medications aim to treat the specific symptoms patients are experiencing due to their depression. Cognitive-behavioral therapy concentrates on negative thoughts and emotions associated with different experiences. Then with counseling sessions it helps patients overcome their negative thoughts and feelings in order to change their behavior. Psychodynamic therapy focuses on unconscious processes that cause patients to have certain behaviors. It aims at making patients aware of past experiences that influence present behaviors in order to resolve the past conflicts and overcome the adverse behaviors (Ebert, Loosen, Nurcombe, & Leckman, 2008).

Medications are available to treat symptoms associated with depression. Selective-serotonin reuptake inhibitors (SSRIs) are the first line medication for depression (Domino, 2012). These medications increase serotonin, which regulates mood, pain perception, and gastrointestinal function. Some medications are serotonin and norepinephrine reuptake inhibitors (SNRIs), which cause an increase in serotonin as well as norepinephrine, both of which regulate mood. Tricyclic antidepressants also work by increasing serotonin and norepinephrine (Murphy, Cowan, Sederer, 2009).
Patients who do not adequately respond to initial treatments have options available to try to maximize symptom improvement. A combination of cognitive-behavioral therapy, psychodynamic therapy, and medications can be used. The frequency of cognitive-behavioral therapy and/or psychodynamic therapy can be increased. Also medications come in different doses, so if lower doses of medications are not treating the depression adequately, then the dose can be increased to the maximum approved dose. Different medications are available, so if one medication is not relieving depressive symptoms, then the patient can be switched to a different medication. In addition, a combination of medications can be used (Murphy, Cowan, Sederer, 2009). Response to treatment is based on remission. Remission is the primary goal of depression treatment; remission means patients are asymptomatic or back to their baseline. Remission does not mean the patient has complete absence of symptoms, but that they have no more than minimal symptoms (Muller et al., 2006). Now with research pointing towards inflammation contributing to depression, anti-inflammatories may have a role in the treatment of depression resistant to current treatment options. Studies testing for the efficacy of anti-inflammatory medications as adjunctive therapy with standard medications for the treatment of depression have yet to be produced in the United States; however, other countries have researched anti-inflammatory medication effects on depression.

In Germany, Muller et al. (2006) studied the effects of reboxetine, a noradrenergic antidepressant drug that inhibits only the reuptake of norepinephrine, used in combination with celecoxib, a COX-2 inhibiting anti-inflammatory versus reboxetine with a placebo in patients with major depression. Major depression
diagnosis was based on the Hamilton Depression Scale (HamD), 17 item version, and scores of the patients ranged from 15 to 38. The study concluded that there was a statistically significant decrease in depressive symptoms seen among both groups; however, there was a much greater decrease in symptoms in the group that received the celecoxib with reboxetine. The group receiving the celecoxib had a mean decrease of 15 HamD points; whereas, the placebo group only had a decrease of about 8 HamD points. In addition, remission of the patients was tested at 6 weeks after treatment. Remission was met when patients scored \( \leq 7 \) points on the HamD scale. Forty-five percent of patients receiving reboxetine and celecoxib were remitted at 6 weeks, and only 20% of the reboxetine and placebo patients were remitted at 6 weeks. There was not a significant difference in side effects seen among the different groups either (Muller et al., 2006). So this study supports better outcomes for patients receiving an anti-inflammatory medication in conjunction with typical anti-depressant treatment, without increased side effects.

Fluoxetine, a selective serotonin reuptake inhibitor, is widely used in the United States to treat depression. In Iran, Akhondzadeh et al. (2009) tested fluoxetine with a placebo versus fluoxetine with celecoxib in patients diagnosed with major depressive disorder based on the HamD scale. Major depression was based on patients having a score of 18 or greater on the HamD scale. Fifty percent of the patients in the fluoxetine and placebo group had a reduction in their HamD scores at the end of the 6-week trial, and 90% of the patients in the fluoxetine and celecoxib group had a reduction in their HamD scores. There proved to be a significant difference between those patients in remission among the fluoxetine with placebo group versus the fluoxetine and celecoxib
group at the end of the trial. Only 5% of the patients in the fluoxetine and placebo group were in remission after 6 weeks, while 35% of the fluoxetine and celecoxib group were in remission. Once again there was not a significant difference in side effects seen among the different groups. Specifically, no cardiovascular events or side effects were reported or seen by ECG in the fluoxetine and celecoxib group (Akhondzadeh et al, 2009).

**Implications to Physician Assistants’ Practice**

Depression affects a wide range of patients, and it can present in patients with different medical illnesses. It is important that physician assistants are able to recognize the symptoms of depression in patients, correctly make the diagnosis, and treat the patient accordingly. Physician assistants are trained to work in primary care. Depression is generally diagnosed, treated, and managed in primary care, so it is essential that physician assistants are familiar with depression. Also, patients receiving care from specialists may have depressive symptoms. So, physician assistants working in these areas also need to be aware of the presenting signs. Then they can direct the patient to a physician or physician assistant who can treat and manage their depression.

Physician assistants need to be able to identify the signs and symptoms of depression in patients. Then, clinicians should have tools available to them, such as self-reporting or clinician administered questionnaires that can allow the clinician to screen for depression in patients who present with symptoms related to depression. Also, it is crucial that physician assistants know the criteria to diagnose depression based on the *Diagnostic and Statistical Manual of Mental Disorders*. With the newly
presented research, clinicians can use CRP or IL-6 to help support the diagnosis of depression. If these markers are elevated, the diagnosis of depression is supported better in the patient. If the markers are within normal limits, then other illnesses accounting for the symptoms may need to be explored more thoroughly.

After the physician assistant has diagnosed the patient with depression, it is inherent that the patient receives the correct treatment. Cognitive-behavioral therapy, psychodynamic therapy, and medications remain as the basic treatments for depression. Some patients can adequately be managed in primary care by physician assistants and physicians; however, other patients are resistant to standard treatments in primary care. These patients should be referred to a specialist, such as a psychologist and/or psychiatrist. Yet, even with specialists managing patients’ mental illnesses, therapy modifying patients’ behaviors, and different classes of medications correcting chemical imbalances, some patients continue to have depressive symptoms. After all the conventional treatments have been exhausted, anti-inflammatory medications should be considered in patients resistant to treatment. The risks and benefits should be discussed with the patient, and if the benefits outweigh the risks then an anti-inflammatory, such as celecoxib could be started in the patient. Then physician assistants could monitor and document symptoms in the patient. If the symptoms are improving, the anti-inflammatory medication could be continued; however, if there was no shown benefit, then the anti-inflammatory medication could be discontinued.

Depression can be a very debilitating illness to patients, especially those with comorbid illnesses. It is important that patients with depression get adequately treated so they can function better in their daily living. Physician assistants can work in any
area of medicine, so they need to be able to recognize depression because it can present in any environment. A brief intervention with the patient to determine if they may have depression can make a substantial difference in their care. If diagnosing the patient and treating the patient is out of the scope of practice by the physician assistant recognizing the symptoms, then they can get the patient to a clinician who can diagnose and treat the patient. Adequate treatment of depression is essential for improving the overall health of the patient.
Chapter 3: Conclusion

The role of inflammation linked to depression needs to be researched further. Evidence shows there appears to be a link between the two, and it may be possible to support the diagnosis of depression with CRP and/or IL-6 as diagnostic tools. Depression will remain primarily diagnosed clinically; however, it may be able to be supported by an objective diagnostic marker. An objective measure would help to distinguish depression from other illnesses that may have similar symptoms. There are diagnostic tests available for other illnesses, such as hypothyroidism and sleep apnea, which may cause similar symptoms to depression. The tests for those illnesses can rule them in or rule them out when diagnosing a patient. And now with the new emerging evidence, CRP and IL-6 may be available to support depression when other illnesses have been ruled out. More evidence of CRP and IL-6 elevation in depression would strengthen the connection of inflammation with depression and CRP and/or IL-6 as a diagnostic marker for the illness.

Studies in the United States need to be conducted on the efficacy of standard treatments of depression with anti-inflammatory medications. Other countries have shown that anti-inflammatory medications, when used with selective-serotonin inhibitors, increase remission rates in depressed patients. It would be a breakthrough if researchers in the United States conducted similar studies and showed increased remission rates in its population of patients. Then there would be an answer to how to treat patients diagnosed with depression, whose symptoms remain resistant to current standard treatments, and it would lead to better quality of lives for those patients who continue to suffer from the debilitating effects of depression.
References


Abstract

**Objective:** To explore the relationship between depression and inflammation, inflammatory markers as support for the diagnosis of depression, and anti-inflammatory medications as adjuncts to traditional depression treatment.

**Method:** Key search words were used to seek journal articles relating to depression and inflammation, CRP and IL-6 levels in patients with major depression, and anti-inflammatory medications in the treatment of depression. Access Medicine, EBSCO Host, PsycINFO, PubMed, and CINAHL were the main databases used.

**Results:** Two meta-analysis articles, two double blind with placebo controlled trial articles, and four research articles were found to be appropriate to the topics. Additional books and articles were used as supplements.

**Conclusion:** Among individuals diagnosed with major depression, CRP was elevated in depressed males and IL-6 was elevated in depressed females, so these markers can be used to support the clinical diagnosis of major depression. Celecoxib with an antidepressant increased remission rates in patients with major depression.