2018

New Ways of Predicting Efficacy of Antidepressants

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New Ways of Predicting Efficacy of Antidepressants

By

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Scholarly Project

Submitted to the Graduate Faculty of the

University of North Dakota

In partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2018

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ACKNOWLEDGEMENT

I would like to give a special thanks to Dr. Matthew Doppler, PhD and Ms. Amber Entzel for all of their input and help with this scholarly project. Your time and expertise with this topic are greatly appreciated. I would also like to thank all of the patients that I have met in my clinical experiences with a diagnosis of major depressive disorder. You inspired me to choose this topic to try to find new ways to overcome this disorder.

ABSTRACT

Major depressive disorder (MDD) is a neuropsychiatric condition that is becoming increasingly prevalent in our country. According to Cai, Huang, and Hao (2015), MDD is "common and devastating" (p. 61) and has a very complex pathophysiology. Until recently, a definitive etiology had not been found, however, new evidence has suggested that Brain-derived neurotrophic factor (BDNF) and cognitive-emotional biomarkers may be a key into the mechanism of this disorder.

My literature review of articles found in PubMed, CINAHL, Cochrane Library, and PsychINFO within the last ten years focused on the hypotheses of the pathophysiology of MDD, cognitive-emotional biomarkers, and BDNF. The review found that MDD has a multitude of interconnecting systems that highlight its mechanism, and this is why it is so difficult to find a treatment option that works. However, cognitive-emotional biomarkers were able to predict the efficacy of certain antidepressants in the treatment of MDD. BDNF was also found to be decreased in patients with MDD and increased after treatment with certain medications. These systems may help predict better treatment response and an overall improvement of the burden of this disease.

Key Terms: *brain-derived neurotrophic factor, sertraline, venlafaxine, venlafaxine hydrochloride, depressive disorder, serotonin and noradrenaline reuptake inhibitors, and serotonin uptake inhibitors*

INTRODUCTION

MDD, according to Cai et al. (2015), "is a mental disorder characterized by prominent and persistent low mood, mental retardation, cognitive impairment, volitional decline, and somatic symptoms" (p.61). The Centers for Disease Control and Prevention (2016) states that almost 10% of adults aged 40-59, and more than 1 out of 20 Americans 12 years of age and older reported current depression. Up until this point, there has not been a clear etiology of this disorder. In the last decade, there has been an abundance of research showing that levels of neurotrophins, such as BDNF in the brain, may be involved in the pathophysiology of MDD and may accurately predict the efficacy of antidepressant medications and the remission of depression. The purpose of this review is to determine how BDNF and cognitive-emotional biomarkers factor into the pathophysiology of MDD, and if they can accurately predict the efficacy and outcome of certain antidepressants.

STATEMENT OF PROBLEM

According to Cai et al. (2015), "MDD can reduce the capacity of a patient to study, work, and engage in social skills" (p.61). It can also increase the risk of suicide and disability rate and has a very high recurrence rate. According to the World Health Organization, there were 300 million patients with MDD in 2015. "It is estimated that by 2020, the disease burden caused by MDD will be ranked next to ischemic heart disease, becoming the second most common cause of disability and death" (Cai, 2015, p.61). The etiology of MDD has not been completely understood, according to Ristevska-Dimitrovska et al. (2013), and many new hypotheses in the pathophysiology of MDD have been formulated. Not having a definitive mechanism by which this disease works makes it harder to find treatment options that are going to provide the efficacy

and tolerability that these patients need. As more definitive mechanisms are discovered,

treatment options can be more effective as they are tailored to the specific mechanism.

RESEARCH QUESTIONS

In adults with MDD, does BDNF play a role in the pathophysiology of MDD?

In treatment of adults with MDD, do cognitive biomarkers predict the efficacy and

outcome of treatment and remission?

In treatment of adults with MDD, does BDNF predict the efficacy and outcome of

treatment and remission?

METHODOLOGY

For my scholarly project, I utilized PubMed, CINAHL, Cochrane Library, and

PsychINFO to collect pertinent information regarding cognitive markers and BDNF and their

affiliation with depression. Within these databases, I used the following search terms: brain-

derived neurotrophic factor, sertraline, venlafaxine, venlafaxine hydrochloride, depressive

disorder, serotonin and noradrenaline reuptake inhibitors, and serotonin uptake inhibitors, in

various combinations, to generate research. In PubMed, CINAHL, and PsychINFO, MeSH terms

were used. I focused on peer-reviewed articles, including studies and reviews that were

published within the last 10 years.

LITERATURE REVIEW

A review of the literature showed that BDNF is reduced in patients with MDD. It has also

been shown to increase in response to certain antidepressants. Cognitive and emotional

biomarkers were also shown to increase the efficacy of antidepressant treatments. The primary

goal of treatment for MDD is to reach remission, which Kurita, Nishino, Kato, Numata, and Sato (2012), defined "as the absence of significant signs or symptoms" (p.1). These neuronal biomarkers may be the key to improving remission rates upon patients with MDD, and to finally be closer to a definitive cure of this disease.

Pathophysiology of Major Depressive Disorder (MDD)

MDD is diagnostically classified under The Diagnostic and Statistical Manual of Mental Disorders. It states that "MDD presents with at least 5 of the following 9 symptoms: depressed mood or anhedonia (patient must have at least 1; present most of the day nearly every day for a minimum of 2 consecutive weeks), sleep disturbance, change in appetite or weight, psychomotor problems, lack of energy, poor concentration, feelings of worthlessness or guilt, and suicidal ideation." The symptoms need to "cause clinically significant distress or impairment in social, work, or other areas of functioning", and the episode cannot be "attributable to the physiologic effects of a substance or other medical disorder" (ClinicalKey, 2017).

According to Cai et al. (2015), the understanding of the pathophysiology of Major Depressive Disorder has, up to this point, been mainly based on the monoamine-deficiency hypothesis. This hypothesis "proposes that the occurrence of depression is associated with deficiencies of three major monoamine transmitters, 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA)" (p.61). However, this hypothesis has been seriously challenged in the last few years for a couple of reasons. Antidepressant treatment only has an efficacy of 60-65%, a remission rate of only 30%, and a high percentage of patients that do not show any improvement. Also, antidepressants increase the levels of these monoamine neurotransmitters in the central nervous system (CNS), but it often takes at least two weeks for them to take effect. This evidence suggests that the monoamine deficiency only partly explains

the pathogenesis of depression. This review performed by Cai et al. looks at the new hypotheses that have emerged and offers new thinking in the mechanism behind depression.

Neurotrophic factors are a class of small proteins that include nerve growth factor, BDNF, insulin-like growth factor, and transfer growth factor. Some of the roles of these proteins include "maintaining neural survival in embryonic development and promoting differentiation, facilitating axonal growth, guiding nerve-growth direction, maintaining the survival of mature neurons, and accelerating neurogenesis" (Cai, 2015, p.62). Patients with depression may show atrophy or lack of neurons, most commonly in the hippocampus and cerebral cortex of the brain.

Other hypotheses in the pathophysiology of depression included inflammatory cytokines, the hypothalamus-pituitary-adrenal (HPA) axis, and glutamate receptors. Verduijn et al. (2015) also found that dysregulation of vitamin D may be integrated into the etiology of MDD. Cai et al. (2015) believed that BDNF dysfunction and increased apoptosis are the final common cascades in the pathogenesis of MDD and new therapeutic strategies to enhance BDNF may be an effective action against this disorder.

Rot, Mathew, and Charney (2009) aimed to review data on "how genes, psychosocial adversity in childhood, and ongoing or recent psychosocial stress may impact multiple neurobiological systems relevant to major depressive disorder" (p.305). Rot et al. stated that investigations have traditionally been focused on the monoamine neurotransmitters serotonin and norepinephrine in the pathophysiology of depression. This hypothesis initially postulated that "depressed individuals are likely to have low levels of these neurotransmitters" (p.305), and various antidepressant medication will acutely increase their levels. However, they do not exert their clinical benefit immediately, and for some people do not offer any benefit at all. This suggests that there must be another variable behind the failure of these medications.

Rot et al. (2009) stated that there has not been a specific gene or series of genes found that cause depression, rather, variations in genes, or polymorphisms, may increase the risk of depression. "Genes help control the metabolism of neurotransmitters and their receptors, the numbers of particular types of neurons and their synaptic connections, the intracellular transduction of neuronal signals, and the speed with which all of these can change in response to environmental stressors" (Rot, 2009, p.306). A variation of these genes could cause detrimental effects and is why genetic testing in relation to depression has recently become more popular.

Brain-derived neurotrophic factor "plays a major role in the birth, survival, and maturation of brain cells during development" and "is important for cell growth and for allowing changes in the synapses between neurons (synaptic plasticity) throughout life" (Rot, 2009, p.307). A polymorphism of this growth factor affects the intracellular transport and secretion of BDNF and may increase depression vulnerability. There has also been further evidence from postmortem studies, in which low levels of BDNF have been found in the hippocampus and prefrontal cortex of symptomatic depression patients, as was reported with Cai et al. (2015).

Rot et al. (2009) identified an important downside of many studies on the pathophysiology of depression, in which they tend to focus more on people who are currently depressed. This gives readers a lot of information, however, the data does "not allow for a distinction to be made between cause and effect" (p.305). For example, is the reduction in serotonin synthesis causing depression, or does depression cause a reduction in serotonin synthesis? Is a third factor responsible for both?

It is clear that there is a multitude of interconnected systems that are involved in the pathophysiology of major depressive disorder. This explains why antidepressant treatment frequently does not lead to clinical remission, as most target monoamines. "The exact roles of

the monoamine and other neurotransmitter systems as well as their extracellular, intracellular, local, and regional targets" (Rot, 2009, p.311) of this disorder are continuing to be defined, and a clearer etiology underlying this disorder would help warrant more successful treatment.

Cognitive & Emotional Biomarkers

According to Castellano et al. (2016), it has been shown that MDD is often associated with cognitive dysfunction involving "attention, learning, memory, and executive functioning" (p.1291) and the presence of these cognitive symptoms may predict a decreased response rate to antidepressant medications. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) have shown efficacy for affective symptoms (mood, emotions, or feelings), however, it is unclear if they improve cognitive symptoms. In this prospective, observational, multicenter cohort study, Castellano et al. aimed "to test the hypothesis that SSRIs and/or SNRIs may affect cognitive symptoms in MDD patients and, if so, to evaluate whether or not such an effect is correlated to their effect on affective symptoms" (p.1291).

The 52 MDD patients (mean age 54.7 ± 12.1 years; 39 women and 13 men) involved in the study were recurrent depressive patients and were having an acute depressive episode at the beginning of the study and a recent history (in the last 4 weeks) of having partial response to a previous antidepressant drug. A total of 33 patients (2 left the study due to adverse effects) were assigned to 12-week treatment with an SSRI, including escitalopram (n=14), paroxetine (n=9), sertraline (n=1), and citalopram (n=9). The remaining 16 patients (1 left the study due to adverse effects) were assigned to SNRI treatment with either venlafaxine (n=8) or duloxetine (n=8). The patients underwent cognitive and neuropsychiatric assessments before the switch of pharmacological treatment, and at 4 and 12 weeks of follow-up. The following psychometric

instruments were used to assess cognitive and affective symptoms: Hamilton Depression rating

scale (HDRS) and Beck Depression Inventory (BDI-II) to assess symptoms, and Mini Mental

State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Frontal Assessment

Battery (FAB), Rey's 15 Words Test, and Digit Span to assess cognitive function.

Castellano et al. (2016) found that both SSRIs and SNRIs reduced the affective

symptoms in MDD patients at the end of the 12-week treatment (HDRS score 22.18 ± 7.38 to

12.94 ± 7.93 in the SSRI cohort and HDRS score 18.94 ± 4.58 to 12.55 ± 8.99 in the SNRI

cohort) (BDI-II score from 33.67 ± 11.67 to 20.06 ± 12.78 and from 30.06 ± 8.97 to $20.06 \pm$

12.39 in the SSRI and SNRI cohort, respectively), as well as significantly improved the global

cognitive function (increased scores of both MMSE and MoCA). Both SSRIs and SNRIs

improved executive function (FAB scores) and verbal memory (Rey's 15 Words Test), however,

this improvement was independent from the efficacy of affective symptoms.

Castellano et al. (2016) reported that "a recent study demonstrated that a significant

proportion (over 20%) of MDD patients successfully treated with SSRIs for over 6 months

reported cognitive symptoms including inattentiveness, lack of concentration, and memory

impairment. Therefore, long-term treatment studies with SSRIs and/or SNRIs are needed to

assess whether and how these drugs can differentially affect verbal and working memory in

MDD patients" (p.1296). Other limitations of this study included the length of time of treatment,

as well as the small sample size. Longer observational studies are needed to better understand

how these drugs can differentially affect cognitive symptoms in MDD.

According to Etkin et al. (2015) there are a wide range of treatment options for patients

with MDD, however, "only approximately one-third of patients reach remission with any single

antidepressant" (p.1332). In comparison with Castellano et al. (2016), Etkin et al. stated that

"depression is characterized by perturbations in psychomotor response speed, processing speed, executive functions (eg, attention and working memory), memory encoding, and recall and emotion processing" (p.1332). Etkin et al. performed an analysis on a previous study, termed the iSPOT-D (International Study to Predict Optimized Treatment in Depression) trial. His report, which analyzed data based on a cross-validated multi-variate pattern, assesses whether performance of standardized tests of cognition and emotional capacities predicted remission or response of depressive symptoms.

The iSPOT-D study included 1,008 adults with first-onset or recurrent MDD, as well as 336 healthy controls that were matched in age, gender, and years of education. The participants were randomized to receive escitalopram, sertraline, or venlafaxine-extended release. Study visits occurred at week 0 (pretreatment) and week 8. At these visits, clinician raters completed the Hamilton Rating Scale for Depression (HRSD) and participants completed the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR). For this report, Etkin et al. (2015) defined remission as "either an HRSD score ≤7 or a QIDS-SR score ≤5" (p.1333). Response was defined as "≥50% decrease from baseline in either the HRSD or QIDS-SR score" (p.1333). At baseline, participants also completed a battery of standardized tests to evaluate the range of cognitive and emotional capacities.

Etkin et al. (2015) focused his analyses on patients (n=655) that completed the iSPOT-D trial (taking the randomized medication and having clinical scores at baseline and week 8). Observations showed that "remission rates with escitalopram treatment were higher for individuals predicted to remit with escitalopram (58%) than for those predicted to not remit (16%)" (Etkin, 2015, p.1336), and remission rates were higher if they received escitalopram versus sertraline or venlafaxine (58% vs. 32%, p=0.016). Etkin et al. stated participants that were

predicted to reach remission had slightly lower depressive severity, were more educated, and received a lower dose of escitalopram at week 8. The patients that were predicted not to reach remission had generally impaired cognitive functioning. Those predicted to not remit with escitalopram remitted at a lower rate if they received escitalopram compared with venlafaxine and sertraline (16% vs. 26%, p=0.300).

According to Gyruk et al. (2016), cognitive function and related constructs are defined as "psychological processes that underlie the ability to carry out goal-directed behaviors and modify prepotent responses" (p.274). These abilities enable individuals "to fine tune their behavior across a variety of domains" (p.274). It has been documented that deficits in depression behaviorally across working memory/continuous performance and response inhibition are present. "Neuroimaging studies also show that, compared to healthy patients, depressed patients show altered activation of cognitive function circuitry across a range of tasks that tap into working memory/continuous performance, planning, and inhibition" (Gyruk, 2016, p.274).

In the iSPOT-D trial, neuroimaging data was collected before and after randomized treatment with three commonly prescribed antidepressants: escitalopram, sertraline, and venlafaxine-extended release. Gyruk et al. (2016) performed MRI data analyses of patients included in the iSPOT-D study and focused on 80 previously nonmedicated participants with MDD and compared to 34 age, sex, and education matched healthy controls. Gyruk et al. hypothesized that "neural activation, as assessed by functional MRI scans during 1 or all 3 cognitive task probes (response inhibition [Go/NoGo task], selective attention [oddball task], and working memory updating [n-back continuous performance task]) in medication-free pretreatment in depressed patients would predict antidepressant outcome" (p.275). Analyses also

looked at if the neural signals would interact with specific medication type (SSRI, SRNI), and if they will change with treatment as a function of remission.

A specific cognitive test called the Go/NoGo task assessed response inhibition. In this assessment, it was shown that remitters to treatment were distinguished from nonremitters by greater pretreatment right dorsolateral prefrontal cortex (DLPFC) activation. "MDD patients who remitted were distinguished by relatively normal levels of DLPFC activation pretreatment, which attenuated posttreatment" (Gyruk, 2016, p.279). Patients who did not reach remission showed DLPFC hypoactivation at both pretreatment and posttreatment. A "failure to engage the DLPFC region may be a general marker of nonresponsiveness to treatment" (p.279), as stated by Gyruk et al. A region in the right inferior parietal cortex predicts HRSD remission differentially by SSRIs compared to SNRIs. Regarding effects of medications, Gyruk et al. found that "remitters specifically to SSRIs showed correspondingly normal levels of inferior parietal activation, which also attenuated posttreatment, while nonremitters to SSRIs showed parietal hypoactivation. Thus, SSRI and SNRI responders showed opposing patterns of activation in the parietal cortex" (p.279).

Gyruk et al. (2016) aimed to identify neural predictors of outcomes of treatments and did not compare active to placebo conditions. Further studies will need to be performed to expand the array of antidepressant medication further, as only three medications were looked at. This study also had a relatively small sample size and future studies should be performed to assess in a larger sample group.

Brain Derived Neurotrophic Factor (BDNF)

Begni, Riva, and Cattaneo (2016) defined neurotrophins as "a family of proteins that promote the growth, survival and differentiation of neurons" (p.123). In 1988, it was found that

neuronal cells can secrete survival factors, neurotrophins, which promoted detailed studies. They were "shown to regulate the growth, maintenance and apoptosis of neurons in both the central nervous system (CNS) and the peripheral nervous system (PNS)" (Begni, 2016, p.123). There are four main neurotrophins that are found in mammals, including nerve growth factor (NGF), brain-derived neurotrophic factor, neurotrophin 3 and neurotrophin 4. Begni et al. performed a review of BDNF and its involvement with pathological conditions.

The BDNF gene, as proposed by Begni et al. (2016), was found to be very complex. It consists of multiple 5'-non-coding exons and one coding exon at the 3' end. Certain exons were found to be mostly brain specific, whereas others were expressed in the brain and non-neuronal tissues. Ide et al. (2015) stated that "BDNF is highly expressed in the cortex, hippocampus, limbic structures, cerebellum, and the olfactory bulb" (p.120). Functional roles have been identified for different transcripts of BDNF, such as "alterations of hippocampus-prefrontal cortex circuitry as well as deficits of γ-aminobutyric acid (GABA)-ergic interneurons in the prefrontal cortex" (Begni, 2016, p.124). Of most importance, an alteration of certain BDNF transcripts has been reported in several psychiatric disorders.

BDNF is the most common neurotrophin (Yang et al., 2016) and when secreted, binds to certain receptors and initiates a series of downstream signaling cascades. This leads to the prevention of programmed cell death and neuronal differentiation. Neurogenesis and neuroplasticity are key mechanisms involved in memory and learning, and if this is disrupted, can contribute to severe pathological conditions. BDNF plays a crucial role in brain development and brain plasticity and decreased levels or impaired signaling can offer detrimental effects (Begni et al., 2016).

BDNF as a Target for Treatment Intervention

BDNF has been proven to be low in patients with MDD, however, it is still unclear the exact mechanism behind how it works. Wolkowitz et al. (2011) aimed to "determine whether serum BDNF levels are low in un-medicated depressed subjects compared to matched healthy controls, whether serum BDNF levels increase in response to antidepressant treatment, and whether baseline serum BDNF levels and treatment-associated changes in serum BDNF levels are related to concurrent depression ratings" (p.1624).

Thirty subjects were included in this study that had unipolar MDD. The 17-item Hamilton Depression Rating Scale (HDRS-17) was used to assess the severity of depression at baseline and at the end of week 8 of antidepressant treatment. The average baseline of this score was 26.1 ± 8.3. The depressed patients were divided into two separate studies and data was pooled to increase statistical power. The first study involved escitalopram, while the other study looked at sertraline, both SSRIs. There were 15 male patients treated in the escitalopram group for 8 weeks in a single-blind, fixed-order, within-subject cross-over manner. In the second group, 14 depressed patients (9 female, 5 male) were prescribed sertraline in an open-label manner. Two of these subjects dropped out and two did not have complete sets of data. The serum BDNF levels were measured at baseline for all subjects and after 8 weeks of treatment for the depressed patients.

The pre-treatment BDNF serum levels were significantly lower in the 29 depressed subjects versus healthy controls, 14.88 ± 5.41 vs. 20.91 ± 7.07, respectively. The HDRS-17 ratings (baseline $=26.1 \pm 8.3$, week $8=13.2 \pm 8.9$) significantly improved with antidepressant treatment, as well as serum BDNF levels (15.07 ± 5.41 at pre-treatment to 18.75 ± 6.97 at week 8).

Many studies have already examined serum BDNF levels in un-medicated patients with MDD, and nearly all of them have found decreased levels compared to controls. Wolkowitz et al. (2011) results support these previous findings, as well as an increase of BDNF levels over the course of antidepressant treatment. The study also found that subjects with initially higher serum BDNF levels showed a larger antidepressant response to sertraline and escitalopram after 8 weeks of treatment.

According to Matrisciano et al. (2009), BDNF is a neurotrophin that has recently been implicated in the pathophysiology of depression and the activity of antidepressant drugs. It regulates neuronal function across life span and "affects neuronal outgrowth, synaptic connectivity, and neuronal repair" (p.247). "Patients with MDD showed lower serum BDNF levels, which negatively correlated with depression rating scores. The effect on BDNF appears to be variable depending on the brain region, the cell type, length of treatment and the pharmacological characteristic of the drug" (Matrisciano, 2009, p.248). Matrisciano et al. aimed to compare serum BDNF levels in depressed patients versus healthy controls, test the action of three antidepressant medications (sertraline, escitalopram, and venlafaxine) on serum BDNF levels after 5 weeks and 6 months of treatment, and test the association between BDNF serum levels and depression rating scores after treatment.

In this study, 21 subjects (11 males and 10 females) who met diagnostic criteria for MDD and 20 normal controls (9 males and 11 females) were included. The patients were randomly assigned to sertraline, venlafaxine, and escitalopram treatment for 6 months. At the beginning of the trial, blood samples were collected, as well as after 5 weeks and 6 months of treatment. The serum BDNF protein content was measured by ELISA using a commercially available kit. The severity of depression was assessed using the HRSD and severity was defined as remission ≤ 7,

mild depression between 7 and 17, and moderate-severe depression ≥17. This assessment was

done at baseline, 5 weeks, and 6 months.

There were 7 patients that were assigned to each of the three medications. The mean ±

SD of the baseline BDNF serum levels were: sertraline (29.4 ± 12.6), venlafaxine (32.3 ± 14.0),

and escitalopram (44.4 ± 16.4). The control group's baseline BDNF score was 64.1 ± 13.1. The

BDNF levels at 5 weeks were: sertraline (50.6 ± 14.2), venlafaxine (29.1 ± 16.3), and

escitalopram (38.6 ± 14.4). The BDNF levels at 6 months were: sertraline (52.3 ± 12.7),

venlafaxine (54.9 ± 12.2), and escitalopram (41.6 ± 14.1). The HRSD scores at baseline were:

sertraline (19 ± 5.3), venlafaxine (19.4 ± 4.5), and escitalopram (14.3 ± 5.9). With sertraline,

HRSD scores showed 57.1 % of patients had reached remission at 5 weeks and 100% of patients

at 6 months. With venlafaxine, 85.7% reached remission at 5 weeks and 100% at 6 months. With

escitalopram, 100% reached remission at both 5 weeks and 6 months.

Matrisciano et al. (2009) showed that BDNF levels were lower in depressed patients

versus healthy controls. A significant increase in BDNF serum levels after 5 weeks of treatment

with sertraline and after 6 months of sertraline and venlafaxine were present. All three

antidepressants were effective in relieving depression symptoms after 5 weeks and 6 months,

despite their different effects on serum BDNF levels.

The relatively small sample size in this study performed by Matrisciano et al. (2009) may

have limited its ability to determine meaningful differences. The symptom assessments were

only done by HRSD scores and this may have caused missed components in the depressive

syndrome. Also, the difference in age between the controls and the study group may have

affected the baseline BDNF levels. The younger age of the healthy controls may explain the

higher BDNF levels at baseline, however, the role of aging on neurotrophic factors needs more research before assuming this limitation.

According to Ristevska-Dimitrovska et al. (2013), depressive disorder is not completely understood, however, there is evidence that "complex interactions of biological, genetic, psychosocial, and environmental factors" (p.123) are present. "BDNF involvement in depression has been a focus of intensive research for the last decade" (Ristevska-Dimitrovska, 2013, p.123). It is detectable in blood, although its concentration in brain tissue is much higher. It may pass the blood-brain barrier and indicates that serum BDNF levels may reflect the BDNF levels in the brain. In comparison to research found in Matrisciano et al. (2009), Ristevska-Dimitrovska et al. stated that BDNF levels in untreated patients with MDD have been shown to be reduced and are in negative correlation with depression severity. Ristevska-Dimitrovska et al. aimed to "test the effect of antidepressant treatment on serum BDNF levels in patients with a depressive episode" (p.124). Two separate studies in Macedonia and Bulgaria were conducted and results were assessed both individually and integrated.

In the Macedonian study, 23 patients (11 female, 12 male) that were diagnosed with a first depressive episode were included. The severity of depression was assessed with the HDRS. The control group consisted of 23 subjects that were age and sex matched. Patients were then treated with sertraline, paroxetine, or venlafaxine for approximately 8 weeks. In the Bulgarian study, 10 female patients with depression and 10 control subjects were included. In both studies, blood samples were collected at baseline and after patients achieved remission, however, the HDRS scores were only assessed in the Macedonian study.

In the Macedonian study, the following were the results of serum BDNF levels and HDRS scores: BDNF pre-treatment (13.15 ± 6.75), BDNF post-treatment (24.73 ± 11.80),

BDNF controls (25.95 ± 9.17), HDRS before treatment (28.52 ± 4.02), and HDRS after

treatment (7.04 ± 3.15). In the Bulgarian study, the results were: BDNF pre-treatment (26.84 ±

8.66), BDNF post-treatment (30.33 ± 9.25), and BDNF controls (25.04 ± 2.88). In the integrated

study, the results were: BDNF pre-treatment (17.30 ± 9.66), BDNF post-treatment (26.43 ±

11.25), and BDNF controls (25.68 ± 7.76).

In the Bulgarian sample, no statistically significant difference between serum BDNF

levels of depressed patients before and after treatment was found. Limitations to these results

could include the small sample size and the short duration of treatment course, as it was only

three weeks. In the Macedonian sample, there was a statistically significant difference between

serum BDNF levels in depressed patients at baseline, after treatment, and compared to healthy

controls. Antidepressant treatment increased serum BDNF levels in depressed patients that were

close to the healthy controls. In the integrated study, lower levels of BDNF were shown while

depressive symptoms were evident.

There was no statistically significant difference in BDNF levels between patients treated

with sertraline, paroxetine, or venlafaxine. Again, the small sample size is an important

limitation in this study. Another question arises on if serum BDNF levels do reflect levels of

BDNF in the brain. These limitations need to be considered, however, there is promising

evidence showing that BDNF may be an important feature of depressive disorder.

Cattaneo et al. (2010) stated that BDNF is known to play a crucial role "in the

neurodevelopment and the maintenance of adult brain homeostasis through regulation of

neurogenesis and neuronal plasticity" (p.103). There have been several studies that have

suggested an involvement of BDNF in the pathogenesis of major depression(MD). Meta-

analyses have shown that BDNF in the serum was significantly decreased in drug-free patients

with depression. It has also been shown that pharmacological and non-pharmacological antidepressant treatments have induced normalization of BDNF blood deficits (Cattaneo et al., 2013).

In comparison to Ristevska-Dimitrovska et al. (2013), Cattaneo et al. (2010) stated that blood BDNF may derive from brain production and crossing the blood brain barrier, but it can also be synthesized from different peripheral cells, "such as vascular endothelial cells, smooth muscle cells, in addition to leukocytes" (p.104). Leukocytes have been shown to express genes that encode neurotransmitter receptors and transporters, stress mediators, cytokines, hormones, and growth factors. This has proved similar to brain cells and may be a useful model to study mental illness. "Altered mRNA levels of genes encoding dopamine and glucocorticoid receptors, the serotonin transporter, the transcription factor cAMP response element-binding protein (CREB), and other genes involved in calcium signaling have been found in the peripheral leukocytes of MD patients (Cattaneo, 2010, p.104).

Cattaneo et al. (2010) evaluated whether leukocyte BDNF gene expression was altered in MD patients compared to control subjects. They also aimed to observe the changes in BDNF gene expression during 12-week treatment with escitalopram and assess whether changes in BDNF mRNA levels would correlate with BDNF protein serum content. Twenty-one patients (17 females, 4 males), age 18-65 years, were included in this study, as well as a control group of 16 females and 7 males. The patients were treated with escitalopram over a 3-month period. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to assess illness severity at baseline, and at weeks 8 and 12 of treatment. Blood BDNF samples were collected at the same time of clinical evaluation.

BDNF serum and mRNA leukocyte levels in controls and in depressed patients were expressed as mean ± standard deviation. The serum BDNF values for control, baseline, after 8-week treatment, and after 12-week treatment are 40.92 ± 10.05, 30.58 ± 9.13, 31.92 ± 8.58, and 41.38 ± 10.49, respectively. The mRNA leukocyte levels for control, baseline, after 8-week treatment, and after 12-week treatment are 1.01 ± 0.22, 0.48 ± 0.18, 0.57 ± 0.25, and 1.02 ± 0.15, respectively. The BDNF serum and mRNA leukocyte levels showed a significant decrease in the MD patients compared to controls, as well as increased the level past baseline with escitalopram treatment. The MADRS scores at baseline, week 8, and week 12, showed the following values, 21.42 ± 3.17, 11.23 ± 7.07, and 7.23 ± 5.15, respectively. The drug treatment improved symptoms and significantly decreased MADRS scores. There was no correlation observed between baseline BDNF levels in the serum and leukocytes and severity of illness, as measured by MADRS.

Ghosh, Gupta, R., Bhatia, Tripathi, and Gupta (2015) state that increases in BDNF in the hippocampus of the brain have been reported in multiple human and preclinical studies, however, the mechanistic and therapeutic significance of this is still uncertain. With the emergence of many newer antidepressant medications, it is even more difficult to select an optimum therapy. Ghosh et al. states that there have been recent studies showing that SNRIs, which enhance norepinephrine and serotonin, may result in higher response and remission rates than SSRIs, which only increase serotonin. This randomized, open label, prospective, observational study was carried out to "compare and correlate the clinical efficacy, safety profiles, and plasma BDNF levels in patients" (Ghosh, 2015, p.38) with MDD treated with fluoxetine, a SSRI, and desvenlafaxine, a major active metabolite of the SNRI venlafaxine.

In this study, 60 patients aged 18-60 years with a diagnosis of moderate to severe MDD were included. The Hamilton's 21 item depression rating scale (HAM-D) was used to clinically evaluate depression at baseline, 6 weeks, and 12 weeks, and BDNF plasma samples were obtained at baseline and at week 12 of treatment. The patients were than divided into two groups and randomly assigned to either treatment with fluoxetine or desvenlafaxine.

In the fluoxetine group, there were 19 patients with moderate depression (HAM-D score 15-20) and 11 with severe depression (HAM-D score >20). The mean HAM-D score at baseline was 19 ± 4.09, which was reduced to 12.2 ± 4.58 at six weeks post treatment, and further reduced to 9.24 ± 3.98 at 12 weeks post treatment. The mean BDNF level at the start of treatment was 775.32 ± 30.38 and increased to 850.3 ± 24.92 at 12 weeks post treatment.

In the desvenlafaxine group, there were 22 patients with moderate depression and 8 with severe depression. The mean HAM-D score at baseline was 18 ± 3.75, which reduced to 13.5 ± 3.86 at 6 weeks and further reduced to 10 ± 3.75 at 12 weeks. The mean BDNF level at the start of treatment was 760.5 ± 28.53 which increased to 845.8 ± 32.82 at 12 weeks post treatment. Ghosh et al. (2015) found that plasma BDNF levels increased in MDD patients after 12-week treatment with both desvenlafaxine and fluoxetine.

Kurita et al. (2012) stated that there are two groups that exist among MDD patients: "a group that responds to treatment (the responder group) and a group that is refractory to treatment (the non-responder group)" (Kurita, 2012, p.1). This naturalistic study examined BDNF levels in patients who reached remission and non-responder groups. The changes in plasma BDNF were compared among these two groups.

As with Cattaneo et al. (2010), the MADRS was used to assess the severity of depression. A score of at least 18 represented inclusion criteria. Non-responders were defined as those

refractory to treatment, showing a <50% reduction in MADRS score from the depressive symptom stage. Patients in remission were defined as those with an improvement of symptoms and a MADRS score ≤ 8 after treatment. From a total of 110 patients, 79 were selected for inclusion based on the severity of illness. The patients were categorized into two groups: a remission group and non-responder group based on definitions described earlier. Thirty-one patients were excluded because they either ceased treatment within three months, received intermittent treatment, or showed response with incomplete remission. 38 subjects in the remission group (19 men and 19 women) and 10 subjects in the non-responder group (3 men and 7 women) were included in the final analysis.

A wide range of antidepressants were administered to each group and included amitriptyline, clomipramine, fluvoxamine, imipramine, maprotiline, milnacipran, paroxetine, sertraline, sulpiride, trazadone, amoxapine, aripiprazole. The plasma BDNF levels were measured at the depressive syndrome stage, response stage, and remission stage. The period from the depressive syndrome stage to the response stage was 7.2 ± 8.6 weeks, and the period from the depressive syndrome stage to the remission stage was 12.3 ± 12.6 weeks. The treatment period that was selected for the non-responder group and remission group was 8 weeks. The period-matched depressive symptom/remission time frame was approximately 12 weeks in the non-responder group.

In the remission group, the MADRS score before treatment and at time of response and remission after treatment were 33.7 ± 8.9, 10.9 ± 5.9, and 5.0 ± 2.4, respectively. The plasma BDNF levels in the depressive syndrome, response, and remission stages were $1,827 \pm 1,340$, $2,402 \pm 1,610$, and $3,158 \pm 2,033$, respectively.

In the non-responder group, the MADRS score at the depressive syndrome stage, and at 8 and 12 weeks after treatment were 35.1 ± 6.5, 25.8 ± 7.7, and 35.2 ± 11.4, respectively. The plasma BDNF levels in the syndrome, and 8 and 12 weeks after treatment were $2,932 \pm 2,373$, $2,117 \pm 2,042$, and $1,619 \pm 1,698$, respectively.

In the remission group, the MADRS scores reduced significantly over the course of treatment and the BDNF levels increased significantly with clinical improvement. Patients in the non-responder group did not show much difference in the MADRS scores, however, the plasma BDNF levels were still significantly decreased during the syndrome's 8-12-week period and may prove that it is "an important biomarker for the prognosis of MDD" (Kurita, 2010, p.5).

The disagreement of the period of remission in responders and non-responders is a limitation of naturalistic studies. The other limitation was the variation in drug treatment that was used between the two groups, as well as the amount of medications used. The effects of antidepressants on BDNF levels appear to not be uniform in this study.

DISCUSSION

It is clear that MDD is a very complex disorder. There are many pathways involved in the pathophysiology and this makes it difficult to find treatment options that will work for patients. There have been newer hypotheses in the pathophysiology of MDD that have been highlighted in the last couple of years. The literature has shown that BDNF and cognitive-emotional biomarkers may be important factors in this disorder. The following section is a discussion of the review of literature, focusing on how BDNF and cognitive-emotional biomarkers are involved in MDD and their role in predicting treatment success and remission.

In adults with MDD, does BDNF play a role in the pathophysiology of MDD?

Both Cai et al. (2015) and Rot et al. (2009) stated that the pathophysiology of MDD has been mainly based on the monoamine-deficiency hypothesis. This hypothesis focuses on decreased levels of serotonin, norepinephrine, and dopamine being the cause of MDD. However, there are antidepressant medications to acutely increase all of these neurotransmitters in the brain, and there is only a small number of patients that actually reach remission. This suggests that there is more to the pathogenesis of depression.

The review performed by Cai et al. (2015) found that the many different hypotheses behind the pathogenesis of MDD are "complimentary and mutually linked" (p.70). Genetic and environmental factors, including stress, seem to "initiate a cascade of neurobiological changes that disrupt a dynamic system" (Cai et al., 2015). Glutamate dysfunction, an increase in inflammatory cytokines, an imbalance of the HPA axis, and decreased monoamines all seem to lead to a decrease in BDNF and synaptic plasticity, as well as an increase in apoptosis. These two things seem to be the common pathway in depression, as reported by Cai et al.

Rot et al. (2009) focused on the genetic and environmental factors that Cai et al. (2015) found to initiate neurobiological changes with MDD. Rot et al. found that genes help control neurotransmitter metabolism and environmental stressors can change the speed of neuronal signaling, and interruptions of both of these processes can lead to depression. This review also found that a polymorphism of BDNF may increase depression vulnerability.

Begni et al. (2016) stated that neurotrophins, such as BDNF, regulate growth and apoptosis of neurons in the CNS and PNS. If BDNF levels are decreased, an impairment of brain development and brain plasticity will occur. Yang et al. (2016) stated that neurogenesis and neuroplasticity are mechanisms involved in memory and learning, and if disrupted as with decreased BDNF levels, MDD may occur. Begni et al. also stated that decreased levels of BDNF

"may be one of the consequences of a genetic background of vulnerability, as well as of exposure to adverse environmental events" (p.130). In comparison to Cai et al. (2015), Begni et al. stated that "inflammation, neurotransmitter dysfunction, and altered HPA axis function, may affect BDNF function, leading to deficits in synaptic and neuronal plasticity and enhanced vulnerability to developing several neuropsychiatric disorders" (p.130).

Begni et al. (2016) stated that in 2006, the neurotrophin hypothesis of depression was proposed, which suggested that "a deficiency in neurotrophin levels may contribute to cell atrophy in selected brain areas of MDD patients" (p.129). Studies have established the ability of BDNF to promote antidepressant effects in rats after infusion into the hippocampus or lateral ventricles of the brain. A number of human postmortem studies have demonstrated lower BDNF expression in MDD patients, as well as decreased signaling in the hippocampus and prefrontal cortex. Yang et al. (2016) stated that neuroimaging of depressed adult patients demonstrated the "involvement of decreased neurogenesis in the underlying pathophysiology of MDD" (p.72). Caldieraro et al. (2017) reported that since the introduction of the neurotrophin hypothesis, BDNF "has become one of the most widely-studied biomarkers" (p.46) of MDD and the mechanism behind it is currently considered "one of the central elements in the pathophysiology" (p.46) of depression. It is obvious that other studies share the same thought.

In treatment of adults with MDD, do cognitive biomarkers predict the efficacy and outcome of treatment and remission?

"Cognitive deficits are considered as key symptoms of clinical depression that are associated both with suboptimal response to antidepressants and reduced remission rates" (Castellano, 2016, p.1295). In the study performed by Castellano et al., it was found that both SSRIs and SNRIs reduced affective symptoms in MDD patients after 12 weeks of treatment, as

well as improved cognitive function, however the improvements were independent from each other. This suggests that affective and cognitive symptoms should be considered as different pathological dimensions of MDD. Castellano et al. stated that "imbalance or deficiency in serotoninergic and/or noradrenergic systems has been found to contribute to cognitive deficits" (p.1296), and this may help guide the efficacy of certain medications in the treatment of patients with MDD.

The analysis performed by Etkin et al. (2015) showed that participants were categorized into two subgroups based on their cognitive and emotional test performance. The 'intact' subgroup was "composed of approximately ¾ of the MDD participants who performed on average within the healthy range" (p.1336). The 'impaired' subgroup included "participants with a test performance well below the healthy norm for 11 of the 13 aspects of function" (p.1336). It was shown that the impaired subgroup was older, less educated, and had greater depressive severity than the intact group. The intact group had a better overall response to treatment.

Etkin et al. (2015) found that "response with antidepressant medication can be reliably predicted for outpatients with MDD by their pretreatment performance on a standardized test battery of cognitive and emotional function", however, "this prediction was only evident in a subgroup of participants who had impaired performance across these tests relative to other depressed participants and healthy controls" (p.1340). Patients in the impaired subgroup were shown to have worse treatment response, however, this outcome was able to be predicted and may offer a valuable tool in predicting treatment outcome.

The iSPOT-D trial that was analyzed by Etkin et al. (2015) was also analyzed by Gyruk et al. (2016), however Gyruk et al. analyzed MRI data performed during this trial. As stated earlier, the results showed that activation in the frontoparietal region of the brain predicted

remission with antidepressant treatment, particularly SSRIs. In comparison to Etkin et al., Gyruk et al. found that patients who reached remission were younger in age, however, their years of education did not make a difference with Gyruk et al.

It is clear that there are a few different cognitive biomarkers that have proven to predict the outcome of certain antidepressants. This may offer a new development in the treatment of MDD, however, these three studies analyzed different things and more studies with larger number of subjects will need to be performed.

In treatment of adults with MDD, does BDNF predict the efficacy and outcome of treatment and remission?

The neurotrophin hypothesis of depression theorized that "certain central BDNF deficiencies underlie depression, and that antidepressants work via restoration of central BDNF activity" (Wolkowitz et al., 2011, p.1623). There have been several studies that have found low serum BDNF levels in un-medicated depressed patients, and that these levels increase with antidepressant treatment. The question arises on if BDNF has a role in the etiology of depression or if it has more of a role in the mechanism of action of antidepressants (Wolkowitz et al., 2011).

Wolkowitz et al. (2011) found supporting results with low BDNF in depressed patients. The study also found that BDNF levels increased over the course of antidepressant treatment with sertraline and escitalopram. Wolkowitz et al. stated that there is greater evidence to support that BDNF may be a target of antidepressant action versus in the development of depression itself, as BDNF signaling is necessary for antidepressant effects to occur.

The study performed by Wolkowitz et al. (2011) also found that patients with initially higher serum BDNF levels showed a larger antidepressant response to sertraline and escitalopram. Patients with higher pre-treatment serum BDNF levels may be either less

depressed, or may already be nearing remission, and this may predict an enhanced response to SSRI antidepressants, however, larger studies need to be replicated before confirmation of these findings can occur.

In comparison with results found by Wolkowitz et al. (2011), Matrisciano et al. (2009) also found that BDNF levels were lower in depressed patients. In this study, an increase of BDNF levels after treatment with either sertraline or venlafaxine occurred, however, escitalopram did not increase levels. It is interesting to note that in the study performed by Wolkowitz et al., escitalopram increased BDNF levels, in contrast to findings by Matrisciano et al. This may be due to the pooling of data that occurred and results may have been different if they were divided.

The study performed by Matrisciano et al. (2009) also found an important difference in the effects of BDNF at different time intervals with the antidepressant treatments. The different timing of BDNF increase could be due to the different mechanism of action of these medications and the contribution to the multitude of BDNF production. There was also a "significant association between the increase in BDNF serum levels and the decrease in HRSD scores at endpoint, indicating that a higher percentage increase of BDNF serum levels correspond to a clinical remission from depressive symptoms" (Matrisciano, 2009, p.252).

A study performed by Ristevska-Dimitrovska et al. (2013) again found similar results to Wolkowitz et al. (2011) and Matrisciano et al. (2009), in which low levels of BDNF were shown with MDD patients. One part of the study by Ristevska-Dimitrovska et al. found that BDNF levels increased after treatment with sertraline, paroxetine, and venlafaxine. These results again correlate with previous findings of other studies with sertraline and venlafaxine. As patient's symptoms improved with antidepressant treatment, the BDNF levels increased significantly.

Ristevska-Dimitrovska et al. shows that chronic antidepressant treatment can significantly increase BDNF levels in patients with depressive disorder when patients achieve remission. "A low serum BDNF level may be an important feature of depression" (Ristevska-Dimitrovska, 2013, p.126).

Cattaneo et al. (2010) took a different approach in his study and evaluated leukocyte BDNF. The study compared this to serum BDNF, as well as the effects of treatment with escitalopram. The results showed decreased serum and leukocyte BDNF levels in MD patients, as well as an increase in BDNF levels after treatment with escitalopram.

According to a meta-analysis performed by Sen, Duman, and Sanacora (2008), there is an overwhelming amount of evidence that shows reduced serum BDNF levels in depressed patients and that these levels normalize after antidepressant treatment. Cattaneo et al. (2010) states this may suggest "that BDNF serum fluctuations may reflect neurotrophic disturbances in limbic regions and restoration processes induced by antidepressant treatment (p.106). Cattaneo et al. found new evidence that BDNF mRNA levels in leukocytes were also reduced in MD patients and were increased to levels similar in controls during treatment with escitalopram. It was also found that an increase in these levels was associated with amelioration of symptoms.

A limitation to Cattaneo et al. (2010) focuses on the fact that "BDNF blood alterations are not specific to MD" (p.107). It has been found that other psychiatric disorders, including bipolar disorder, schizophrenia, and eating disorders, also demonstrate this finding. It is not considered a marker of illness. However, it does connect a common pathophysiological mechanism to these disorders, in which BDNF is linked to deregulation of synaptic plasticity. It "may also provide some insight into the high rates of comorbidity that exist between many of the disorders" (Cattaneo, 2010, p.107).

Another limitation to Cattaneo et al. (2010), is that a differentiation cannot be made of whether a BDNF increase observed during escitalopram treatment is due to the medication or from an improvement of depressive symptoms. Ristevska-Dimitrovska et al. (2013), found an increase with sertraline, paroxetine, and venlafaxine and Matrisciano et al. (2009) found an increase with sertraline, escitalopram, and venlafaxine. All three studies demonstrated an improvement of depressive symptoms, however, two different methods were utilized in assessing those scores. A larger study comparing these three medications will need to be performed to accurately differentiate the cause of the increase in BDNF.

Ghosh et al. (2015) compared the efficacy, safety, and plasma BDNF levels of MDD patients treated with fluoxetine and desvenlafaxine. This study found that plasma BDNF levels increased after 12-week treatment with both of these medications. In comparison with Matrisciano et al. (2009), the efficacy and safety profile of desvenlafaxine and fluoxetine is comparable in patients with MDD.

Both antidepressant medications significantly increased BDNF levels, however the small sample size in this study severely limits the results. In previous studies in this category (Cattaneo, 2010; Matrisciano, 2009; Ristevska-Dimitrovska, 2013; Wolkowitz, 2011), the serum BDNF levels have been measured, in contrast to Ghosh et al. who measured the plasma BDNF levels. Some studies have mentioned that plasma BDNF may be a better reflection of brain BDNF levels, but more studies are needed to prove this observation.

Ghosh et al. (2015) also mentions that there were 26 patients that responded to treatment with fluoxetine (4 non-responders) and 27 who responded to desvenlafaxine (3 non-responders). The responders to treatment had higher pre-treatment BDNF levels than non-responders, which compares to research found with Wolkowitz et al. (2011) in which higher BDNF levels, initially,

showed a larger antidepressant response. The post treatment values were greater in the responder groups of both medications as compared to the non-responder group.

Kurita et al. (2010) aimed to investigate responders and non-responders more thoroughly. This study compared plasma BDNF levels in patients that reached remission and those that did not. Kurita et al. found that the plasma BDNF levels in the non-responder group decreased over time. He stated that it has been shown that BDNF levels will increase by antidepressants, environmental enrichment, and modest exercise, and are decreased by stressful events. This information suggests "that the ability of stress to decrease BDNF levels may be greater than the ability of antidepressants to increase BDNF levels" (Kurita, 2010, p.6). Also, if a person looks at the levels of BDNF in the remission versus non-responder group, it can be noted that they are higher in the non-responder group as well as in the depressive syndrome stage, which is in contrast to research found with Wolkowitz et al. (2011) and Ghosh et al. (2015). "High plasma BDNF levels during the depressive syndrome stage may be indicative of treatment-resistant MDD patients. Thus, plasma BDNF levels may help the clinician to predict clinical outcome. In particular, if plasma BDNF levels decrease or are unchanged in an individual with regularly measured plasma BDNF, the clinician may need to reevaluate treatment strategy (Kurita, 2010, p.6).

Overall, the review of literature in this subject showed that BDNF levels were decreased in patients with MDD. It also showed that these BDNF levels increase over time with antidepressant treatment with certain medications. These results may offer a tremendous gain in the treatment of adults with MDD and may finally be able to help find treatment options for patients that will work.

APPLICABILITY TO CLINICAL PRACTICE

In clinical practice, MDD is a disease process that will be encountered many times in a provider's career. Whether it is a primary care provider or an emergency room provider, it is a disease process that is seen on a daily basis, both with treatment strategies and as a comorbid condition. It is a disorder that is growing in frequency, however, there are many flaws in the treatment of MDD, as only a small percentage of patients find a treatment option that offers remission. In some cases, it takes years to find a medication option that works for a patient. This can be both devastating and frustrating to both the patient and the provider. It is still unclear of how this disease process works but new hypotheses in the pathophysiology of MDD have become available that may help alleviate the stress of finding treatment options that work.

My research found that both cognitive biomarkers and BDNF may be the key to finding treatment options for patients with MDD faster and more effectively. Based on cognitive and emotional tests performed before antidepressant treatment, studies were able to predict treatment response to certain SSRI's and SNRI's and this may help in clinical practice. It was also found that BDNF is decreased in patients with MDD and certain antidepressants are able to increase this level. Some studies showed that a higher BDNF level showed a larger antidepressant response.

If providers are able to predict whether certain medications will work before starting them, this can alleviate a large amount of stress and frustration. Cognitive and emotional tests performed prior to antidepressant treatment may be an option to predicting if a medication will work. Also, measuring BDNF levels before and during the course of treatment may help providers predict if antidepressant treatment will work much sooner than has previously been possible. Although there is much more research to be done on these two biomarkers, they

provide a good look into the future of MDD and are an exciting step in the right direction

towards successful treatment of this disorder.

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