Etiology and Treatment for Major Depressive Disorder

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Abstract

This literature review examines the etiology of major depressive disorder and possible treatment options for the disease. Major depressive disorder is a disease with a vast prevalence which effects more than 25% of the population. Individuals with major depressive disorder experience symptoms such as anhedonia and worthlessness which can often lead to suicidal thoughts and actions. MDD is an extremely prevalent disease which can cause an individual to experience severe social, work and family impairments. The purpose of the current literature review is to examine potential mechanisms of depression through four main hypothesis based on monoamine neurotransmission, HPA axis, neuroplasticity and the cognitive theory as well as pharmacological treatment for moderate depression and deep brain stimulation for treatment resistant depression.
Major depressive disorder (MDD) is one of the most prominent and debilitating psychiatric disorders in the world. 17% of people in the world have a lifetime prevalence of MDD while 5-9% experience a 12-month prevalence (Eaton et. al, 2008); meaning that 1 in every 4 people will experience some form of depression in their lifetime. In 2012, the economic burden of MDD was $188 billion dollars compared to $131 billion for cancer (Mrazek et. al, 2014). According to the DSM-5, in order to be properly diagnosed with MDD, patients must display 1) depressed mood or 2) loss of pleasure in addition to displaying 5 of the follow symptoms daily within a 2 week period:

1. Significant weight loss or gain or a decrease or increase in appetite
2. Insomnia, the inability to sleep or hypersomnia, excessive sleepiness
3. Psychomotor agitation which are unintentional and purposeless motions that stem from feelings of restlessness displayed through pacing, biting fingernails or hands, and twitching of the hands or legs
4. Fatigue or loss of energy
5. Delusional feelings of worthlessness or excessive guilt
6. Diminished ability to concentrate, think or process information
7. Suicidal thoughts, attempts or plans

MDD symptoms cause significant impairments in work, social, and family as well as other important areas in an individual’s life. In addition, in order to properly classify the diagnosis as MDD, symptoms must not be attributed to substance use or another psychiatric condition (Reynolds & Kamphaus, 2013).

The severity of depression ranges between individuals. Individuals diagnosed with moderate depression appear to be negative and decrease their regular social activity. Individuals
often display work related stress as well as a deteriorated performance at work or school. In addition, individuals with moderate depression normally deny or blame others for their external problems. These individuals rarely have suicidal thoughts and no attempts. The typical treatment for moderate depression is therapy and antidepressant medication. All forms of depression are debilitating however, severe depression is the most impairing and difficult to treat. Individuals with severe depression socially withdraw completely and may become angry, hostile and aggressive towards others. Severely depressed individuals normally have high stress related to work or school and their performance begins to fail. These individuals repress their feelings and often refuse to talk to others and they consider, plan or have had a prior suicide attempt. Due to the severity of the disease, severe MDD is more difficult and burdensome to treat. Often, individuals with severe MDD do not respond to typical antidepressants and therefore are deemed to have treatment resistant depression (Nemeroff, 2007). In the United States alone, 14 million individuals have treatment resistant depression and annual treatment averages $10,592 per patient (Corey-Lisle et. al, 2002). In addition, individuals with treatment resistant depression only have a 20% probability of successfully treating their disease (Corey-Lisle et. al, 2002). The World Health Organization has deemed depression as the most debilitating disease due to its effect on quality of life, in addition to the social and economic burden associated with the diagnosis (Greden, 2001). MDD is predicted to be the number 1 cause of death in the world by 2020 (Mrazek et. al, 2014).

MDD is a prevalent disorder that affects numerous individuals across cultures and age groups. Although depression is one of the most debilitating diseases in the world and despite vast research, the exact etiology of the disease remains unclear. Understanding the etiology of depression is important for prevention and treatment. Research has indicated that there are
several hypothesis that may contribute or lead to depression. The purpose to this literature review is to examine the most common potential mechanisms of depression: monoamine neurotransmission, HPA axis, neuroplasticity, and the cognitive theory as well as the most effective pharmacological and deep brain stimulation treatment.

Pathology of Depression

Monoamine hypothesis

One of the first potential mechanisms for the etiology of depression is the monoamine hypothesis. This hypothesis states that depression is caused by altered levels in one or multiple monoamines (Dean & Keshavan, 2017). Monoamines levels such as serotonin (5-HT), norepinephrine (NE) and dopamine (DA) are altered in patients with depression and regulation of the monoamine levels are imperative for proper cognitive function, mood regulation and emotion (Naio, Maruyam & Shamoto-Nagai, 2017). Although they are identified in the pathology of depression, there exact functions are not well known (Blier, 2016).

A reduction of serotonin metabolites has been found in patients with depression and medications which increase levels of serotonin are proven to be effective antidepressants (Dean & Keshavan, 2017). The monoamine hypothesis proposes that diminished activity of the serotonin signal pathways causes depression. A study conducted by Stockmeier (2003), on brain tissue found that individuals with depression have an increase of serotonin receptors and transporters in their prefrontal cortex and hippocampus however, serotonin binding is decreased. In addition, serotonin binding in the amygdala is correlated to amygdala reactivity associated with negative emotional stimuli (Schneck et at, 2016). Other research has demonstrated that monoamine levels are predetermined genetically before birth through genes. There is also evidence that genetic abnormalities can lead to deficits in the serotonergic transmission system.
The serotonin transporter gene (5-HTTLPR) has been found to affect how quickly and effectively the serotonin transporter functions. Caspi and colleagues (2003) assessed the relationship between 5-HTTLPR and depression by conducting a longitudinal study which followed individuals carrying the short (S) allele and the long (L) allele. The 5-HTTLPR gene has been found to effect the transcription rate of the gene, the short (S) allele transcription rate is less efficient compared to the long (L) allele (Karg & colleagues, 2011). Researchers found that individuals carrying the short (S) allele have an increase in amygdala reactivity due to threatening or stressful stimuli. Therefore, individuals carrying the lower expressive short (S) allele have an increased risk of developing depression after a stressful life event.

Schneck and colleagues (2016) were interested in examining the emotional and cognitive processes related to the 5-HTTLPR gene. Participant’s 5-HTTLPR genotype was determined before the trial. The trial consisted of presenting subjects with pictures of negative emotional faces while an fMRI recorded amygdala activity. Researchers also used a positron emission tomography to examine serotonin binding. Researchers found that individuals carrying one more copies of the short (S) allele 5-HTTLPR have an increased reaction in the amygdala to negative stimuli due to a decrease in binding of serotonin. Therefore, making the 5-HTTLPR gene and serotonin binding a strong predictor of emotional processing and major depressive disorder.

Dopamine plays a significant role in the pathology of depression. The dopamine neurons, located on the mesolimbic pathway, mediate the reward and motivation pathway (Dean & Keshavan, 2017). Researchers have found that deficits in the dopaminergic transmission and the mesolimbic pathway play a role in the pathology of depression. Antidepressants which increase dopamine and successfully treat the disease provide evidence for the role of dopamine in depression. Watt and Panksepp (2009), identified depression as a disorder that results from
deficits in the mesolimbic pathway, where the dopamine neurons are located. Their research found that the mesolimbic pathway experiences a decrease of function in individuals who have experience significant loss or stress. The behavior symptoms of a shutdown mesolimbic dopamine system includes, reduced motivation, decreased energy and anhedonia – all common symptoms of depression. Researchers also found that antidepressants that increase dopamine levels such as bupropion effectively treat depressive symptoms and help regulate mood.

Norepinephrine is also involved in the pathology of depression because of its relation to mood regulation. Stress causes the corticotrophin-releasing factor, located in the hypothalamus, to produce and release norepinephrine which then causes the release of ACTH from the pituitary gland; the pituitary gland then sends a signal to the adrenal gland which then releases norepinephrine and cortisol (Leonard, 2001). Norepinephrine levels are lower in patients with depression and medications that inhibit norepinephrine reuptake and increase norepinephrine secretion have shown to reduce depressive symptoms.

In addition to functioning on individually, serotonin, dopamine, and norepinephrine are all interrelated and effect each other’s connections in the brain. Activation of one of the monoaminergic systems may result in activation of another system. El Mansari and colleagues (2010) found that both NE and dopamine increase the release of serotonin from the dorsal raphe nucleus, while dopamine has been found to inhibit the release of NE from the locus ceruleus. These results indicate that monoamine neurotransmitters do not operate individually but rather the monoamine systems overlap and are connected. Therefore, an alteration in one of these system will most likely result in an alteration in another (El Mansari et al., 2010). Further evidence of the interaction between the monoaminergic systems is demonstrated through the use of combination treatments in which two antidepressant medications are used in order to act on
both norepinephrine and serotonin which results in a broader and more successful treatment of
depression.

HPA hypothesis

Although there is much evidence on the monoamine hypothesis, it is unlikely that altered
levels of monoamines account for all symptoms of depression. Other findings have shown that
depression stems from an imbalance in neural networks which underlie an individual’s response
to stress (Olsson, 2004). Cortisol is a glucocorticoid hormone which is released in response to
stress. Cortisol is released from the adrenal cortex which occurs in the hypothalamic-pituitary-
adrenal (HPA) system. Therefore, in order to properly respond to stress or threatening situations
individuals must have a fully functioning HPA axis (Pytka, 2017). Dysfunction of the HPA axis
is a possible causal factor of depression because it is associated with a hyperactive response to
stress (Yang et. al, 2016). In a healthy individual, activation of the HPA axis leads to secretion of
the corticotrophin-releasing hormone (CRH) and vasopressin from the hypothalamus, which then
activates the release of adrenocorticotrophic hormone (ACTH) from the posterior pituitary gland.
The release of ACTH then triggers cortisol production from the adrenal cortex which then
activates the glucocorticoid receptors (Pytka, 2017; Juruena, Cleare, & Pariante, 2004).

Dysregulation of the HPA axis leads to the release of cortisol in response to lower levels of stress
which would normally not trigger the release of cortisol. Thus, leading individuals to chronically
elevated levels of cortisol (Dean & Keshavan, 2017). Chronic cortisol levels are considered a
marker for HPA axis dysfunction and therefore a possible indicator of depression.

Cerqueira and colleagues (2005), conducted a study on the neurobiological implications
of elevated cortisol levels. Researchers found that chronic stress increases the number of
glucocorticoid receptors which leads to alterations in three areas of the brain, the medial
prefrontal cortex, the hippocampus and the amygdala. The medial prefrontal cortex function includes processing emotions and executive functioning, the hippocampus is involved with memory and the amygdala is involved with emotions. Specifically, alterations in these 3 areas lead to an abnormal response to stress. Since regions of the brains work together, impairments in one can lead to impairments in another. Similar to a road block, the block might not be on the main road but it still has the potential to impact your ability to successfully reach your final destination. For example, chronic stress decreases long-term potentiation in the pathway from the amygdala to the medial prefrontal cortex which increases amygdala reactivity to stress (Davarci and Pare, 2007). This increase in amygdala excitability leads to a hypersensitive response to stress and a decrease in cognitive processing. Overall, high levels of cortisol effect the brains functional connectivity and impair its ability to properly respond to stressful stimuli or situations.

Ridder and colleagues (2005), assessed altered glucocorticoid receptor signaling in mice as a possible etiology of depression. In order to properly mimic the altered glucocorticoid receptor function found in humans, researchers breed mice with under-expressive and over-expressive glucocorticoid receptor. After a forced swim test, researchers found that mice with a 50% gene reduction of glucocorticoid receptor demonstrated increased helplessness after stress exposure and a dysfunctional HPA axis. While mice with over-expression of the glucocorticoid receptor gene showed a reduction in helplessness after stress exposure. Therefore, mice with over-expression of the glucocorticoid receptor gene may represent a stress resistant model while mice with an under-expression of the glucocorticoid receptor gene may represent a model that is more susceptible to depression; similar to patients with MDD. These mice can
be used as model of the underlying biological changes which occur through the HPA axis in individuals with depression.

_Neuroplasticity hypothesis_

One of the brain’s most remarkable abilities is learning and adapting. In order to learn and adapt, the brain must possess plasticity and have the capability to create and eliminate synapses. The factor that controls neuroplasticity is called the brain-derived neurotrophic factor (BDNF). BDNF promotes the survival and growth of new neurons and synapses which are imperative for learning and adaptive behavior. Chronic stress can lead to a decrease in expression of BDNF in the hippocampus, which is one of the brain regions in the HPA axis. Studies have found that BDNF serum levels are reduced in individuals with depression. Taliaz and colleagues (2010) conducted an animal study in order to assess the relationship between BDNF and depressed-like behaviors. By conducting a knockout experiment, researchers were able to reduce BDNF serum levels in the hippocampus. The reduction of BDNF was able to produce depressed-like behavior in the rats, thus suggesting reduction of BDNF as a possible neuropathology of depression. In order to further study the behavior effects of BDNF levels, Grah and colleagues (2014) conducted a study to examine the relationship between BDNF serum levels as a possible predictor of suicide attempts, a behavior often observed in individuals with depression. The researchers found that individuals with suicide attempts had significantly lower levels of BDNF compared to healthy individuals. These results suggest lower levels of BDNF as a potential marker of depression and specifically suicide attempts.

_Cognitive Theory_

The cognitive model of depression, originally presented by Beck, has been adjusted over the years due to the growth of genetic and neurochemical research. Beck has expanded his theory
which now focuses on the genetic and neurochemical factors of depression that effect cognitive schemas and lead to depression (Beck, 2008). The cognitive model is based on the idea that early life trauma or stress can lead individuals to develop a negative cognitive bias which sensitizes them to interpreting future events and situations. Beck refers to this as the “depressed mode” which leads to increased activity in the amygdala. Increased activity in the amygdala leads to increased reaction to negative events and stimuli. Repeated activation of the “depressed mode” ultimately creates a negative cognitive bias results in a defective HPA system which will misinterpret daily stressors as chronic stressors. Lui & colleagues (2017), conducted a study in which they found that social defeat stress caused depression-like behavior in rats and lead to changes in the prefrontal cortex metabolites. Researchers conducted a social defeat procedure in which they introduced “intruder” rats to unfamiliar cages occupied by aggressive rats who asserted physical confrontation with the “intruder” rat. Once the intruder rat demonstrated social defeat behavior such as freezing or submissive posture, it was placed back in its original cage. The social defeat procedure was conducted once a day for 3 weeks. Researchers then conducted a forced swim test to observe anxiety and depressed like behavior which was followed by taking brain tissues from the prefrontal cortex. After examination, researchers found that the induced stress lead to changes in the prefrontal cortex. The prefrontal cortex is the region in the brain responsible for regulating emotional behaviors – excessive stress alters the prefrontal cortex connectivity which is imperative in order for people individuals to have a realistic response to stressful situations (Carlson et al, 2017). In the current study, the proper response for rats would have been to continue swimming rather than giving up while in the water.

There are numerous possible etiologies for major depressive disorder. The pathology of an individual’s depression must first be identified before seeking the most effective treatment.
Some researchers have purposed a unified theory of depression in which the disease manifests itself in response to multiple etiologies rather than just one. All of the possible etiologies mentioned have the common denominator of stress. It is reasonable to assume that anyone can experience depressive symptoms if they are exposed to severe levels of stress. An increased response to stress and reduced neuroplasticity are reciprocally connected with the monoaminergic systems which can lead to alterations in the neurocircuitry of the brain and impair an individual’s ability to respond to stressfully stimuli.

**Pharmacological Treatments**

Depression manifests itself differently in each and every individual and therefore treatment should be personalized from patient to patient. In addition, treatment should aim at full recovery. Antidepressant medication can reduce debilitating symptoms but cannot cure the disease. Therefore, the aim is that patients will have the capability to fully function socially without the debilitating symptoms of depression. Antidepressant medication is used for the treatment of mild to moderate depression. The four main classes of antidepressant drugs are, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), atypical and MAO inhibitors (Ionescu & Papakostas, 2017).

The most commonly prescribed antidepressant drugs are SSRIs. This antidepressant class is considered the safest because it has fewer and less severe side effects compared to other antidepressant drugs. Common SSRIs include Sertraline, which is more commonly known as Zoloft and Fluoxetine which is sold under the name of Prozac. SSRI antidepressants block the reuptake of serotonin by the presynaptic terminal, allowing serotonin to remain in the in the extracellular fluid longer after it is released.
Depressed individuals are often anxious and exhibit symptoms of hostility and range. Hypersensitivity to stressful stimuli often causes individuals revert to aggressive and emotional behavior. Aggressive behavior can manifest itself through threats, verbal intimidation and even physical violence. Treatment of aggressive and violent behavior is essential to enable patients and their family’s to maintain a normal and healthy life. Farnam and colleagues (2017) assessed the effect of Sertaline on patients with aggressive symptoms. They found that Sertaline reduces the severity of depression and aggressive tendencies such as exhibiting physical or verbal anger. SSRIs, such as Sertaline, block serotonin reuptake in brain regions such as the amygdala, which controls emotional responses, which enables patients to response more realistically and less aggressively to external stimuli.

Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are a newer antidepressant which inhibit reuptake of serotonin and norepinephrine, similar to SSRIs. Norepinephrine and serotonin have receptors located throughout structures of the brain which are responsible for stress reaction. SNRIs, such as Duloxetine, are administered with the goal of restoring serotonin and norepinephrine levels which intern should reduce depressive symptoms. Wrobel and colleagues (2017) conducted a forced swim test after administering rats with Duloxetine. Researchers found that Duloxetine reduces depressive behavior, such as immobility time compared to control rats. However, the effect was only seen in rats who had been repeatedly administered Duloxetine compared to rats which had only taken one dosage.

Although depression is a common disease, it manifests itself through different symptoms and side effects. Over 60% of individuals with major depressive disorder report painful physical symptoms (PPS) making depression with PPS is a subcategory of MDD (Kuga and colleagues, 2017). Atsuchi and colleagues (2017), assessed the effects of duloxetine, SNRI treatment, versus
SSRI treatment through a real-world clinical study behavioral symptoms of patients with depression who experience chronic pain. The study consisted of 523 males and females over the age of 20 with MDD who experience PPS. The study was conducted over the course of 12 weeks in which patients with MDD and PPS were given either duloxetine or SSRIs such as escitalopram, sertraline, paroxetine or fluvoxamine. 273 subjects received duloxetine and 250 subjects received SSRIs. Subjects were given the Brief Pain Inventory-Short Form (BPI-SF) and the 17 item Hamilton Rating Scale for Depression (HAM-17) before starting the antidepressant and at 4 weeks, 8 weeks and 12 weeks. At 4 weeks into the study there was no significant difference in BPI-SF and HAM-17 ratings between the two treatment groups. However, by week 12, patients who received duloxetine scores showed greater improvement in the BPI-SF and the HAM-17 compared to subjects who received SSRI treatment. These results suggest that SNRI antidepressants, specifically duloxetine, should be administered to subjects with MDD who are experiencing PPS. However, in both treatment groups, patients who had experienced one major depressive episode showed greater overall improvement then subjects who experience recurrent depressive episodes.

SSRIs and SNRIs are the most common antidepressant drugs administered to patients with MDD however, 40 to 60% of patients with MDD do not respond effectively to these first-line antidepressants (Bauer et al., 2013). Patients with MDD often discontinue taking first-line antidepressants due to negative side effects. 46% to 52% of patients discontinue taking their antidepressant medication within the first 6 months that it is prescribed to them (Sansone & Sansone, 2012). Ashton and colleagues (2005), conducted a survey which found that 60% of individuals discontinued antidepressant medication due to lack of efficacy, were unpleased with side effects such as lack of sexual interest, tiredness, and weight gain. Sexual dysfunction is the
most commonly reported side effect of first-line antidepressants. Over 47% of patients taking these drugs report an inability to have an erection and difficulty reaching orgasm, termed treatment-emergent sexual dysfunction (Thase et. al, 2017). Therefore, switching antidepressant drugs is a common strategy used for patients who are not satisfied with the antidepressant drug that they are taking due to efficacy or side effects.

Atypical antidepressants are administered when an individual is not responding affectively or is experiencing bothersome side effects from SSRIs or SNRIs. Vortioxetine is a successful atypical antidepressant with a multimodal mechanism of action that is different from SNRIs and SSRI treatment. The drugs clinical action is believed to inhibit the serotonin transporter which blocks the reuptake of serotonin and modifies activity of the 5-HT receptors. Vortioxetine is an antidepressant that is commonly used for switch therapy in patients who have not experienced the desired effect of SNRI or SSRI treatment. Montgomery and colleagues (2014), conducted a 12 week study to compare the effects of Vortioxetine verses Agomelatine, both atypical antidepressants, in patients with MDD who did not achieve successful treatment from SNRI and SSRI drugs. Agomelatine was used as the compared drug because similar to Vortioxetine, its exact mechanism of action is different from SNRI and SSRI antidepressants. Researchers conducted a double blind study in which subjects were randomly assigned the drug and neither researchers nor participants knew who had been administered which drug. The Montgomery-Asberg Depression Rating Scale was used to assess subject’s depression levels at week 8 and week 12 during the study. At week 8, 61.5% of subjects taking Vortioxetine showed significant improvement in depressed feelings and symptoms compared to baseline pre-antidepressant compared to 47.3% of the Agomelatine group. By week 12, 69.8% of subjects taking Vortioxetine were successfully responding to the drug compared to 56% successful response
rates of patients taking Agomelatine. Overall results showed that Vortioextine had significantly higher response rates compared to Agomelatine. Individuals also reported significant improvement in family, work and social life while taking Vortioextine. These results demonstrate that both Vortioextine and Agomelatine are used to successfully treat depression, however patients are more likely to respond to Vortioextine.

Jacobsen and colleagues (2015) conducted a similar study in which they compared response rates between two atypical antidepressants, Vortioextine vs. Escitalopram for patients who were experiencing treatment-emergent sexual dysfunction while on SSRI drugs. Researchers used the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) to assess individual’s treatment-emergent sexual dysfunction throughout the course of the study. They found that CSFQ-14 ratings significantly improved in patients taking Vortioextine regardless of age, gender and severity of depression. Less than 5% of subjects reported side effects, however, those that did reported that nausea, headache and dizziness were more significant while taking Vortioextine while irritability, fatigue and anxiety occurred at a higher rate in individuals taking Escitalopram. These results suggest that Vortioextine is a successful antidepressant drug which should be administered to patients experiencing treatment-emergent sexual dysfunction however, it still has negative symptoms.

Monoamine oxidase inhibitor (MOAIs) antidepressant such as Phenelzine block the enzyme that breaks down and metabolizes 5-HT. MOAIs allow 5-HT to be presented longer in the extracellular fluid (Shulman, Herrmann, Walker, 2013). Krishnan and colleagues (2007) studied the effect of MOAIs on individuals with major depressive disorder. Researchers found that patients taking MOAIs had a response rate between 50 and 70% and that the most commonly used MOAIs tranylcypromine, phenelzine, and isocarboxazid were equally effective
in treatment of depression. Although MOAIs have been found to successfully treat depression, they are not often administered because their effects on multiple neurotransmitters cause severe negative side effects. One of the most impairing effects of MOAIs is dietary restrictions. Individuals who are prescribed MOAIs must avoid foods containing tyramine because they will negatively interact with the medication. Tyramine is an amino acid which aids regulation of blood pressure. Foods and beverages which contain tyramine, such as cheese, meat, fish, poultry, fruits, vegetables, beers and soy ingredients must not be consumed when individuals are taking MOAIs. These foods contain high levels of tyramine which interacts with MOAIs and can lead to dangerously high levels of blood pressure and may lead to serious cardiovascular problems.

Overall, the pharmacological approach for treatment of depression is generally successful in milder cases of depression, specifically in patients who have experienced only one depressive episode. There are numerous antidepressants on the market which all work in different ways and present different side effects. SSRIs are the most common antidepressant due to limited side effects and have been found to be the most effective treatment for individuals with aggressive symptoms while SNRIs have been a more effective treatment for individuals with depression who also experience chronic pain. Atypical antidepressants are administered to individuals experiencing treatment-emergent sexual dysfunction. MOAIs are normally the final pharmacological treatment option due to negative side effects. Antidepressants are the first line for treating depression because of the simplistic method of taking an oral pill. The ease of treatment makes antidepressants an effective and attractive treatment for MDD. However, similar to other diseases, the severity of depression varies across patients and some patients do not respond effectively to antidepressant medications due to efficacy or side effects.

Deep Brain Stimulation
In recent years, a more complicated approach to treating depression has emerged called deep brain stimulation. Deep brain stimulation (DBS) is being assessed as an alternative treatment for individuals with treatment resistant depression. Although there is a wide variety of antidepressant medication, treatment is not always effective. Individuals who have failed to show significant improvement to two or more antidepressants are deemed to have treatment resistant depression and must seek alternative treatments. Electroconvulsive therapy (ECT) is often successful in the treatment of treatment resistant depression however, it often produces negative long-term side effects such as memory disturbances and high relapse rates (Sienaret, 2011). Therefore, more recently, researchers have assessed the effectiveness on DBS for patients with MDD. DBS is an intervention which involves implanting electrodes to deliver adjustable and reversible electrical pulses to areas in the brain (Dijk and colleagues, 2012). Research for DBS has emerged more recently and therefore, different brain regions are being assessed as possible target areas.

In order to ensure the safety of DBS, Serra-Blasco and colleagues (2015), conducted a study to evaluate the cognitive functions of patients before and after DBS of the subcallosal cingulate gyrus. 8 treatment-resistant patients participated in the study. The subjects were around the same age in order to avoid age-related differences in cognitive functions. Memory, executive functioning, verbal fluency, language, processing speeds, and attention were assessed 1 year before and after DBS implantation through multiple different standardized neuropsychological tests. Memory was assessed through the Rey Auditory Verbal Learning Test, using delayed and free recall; executive functioning was assessed through the Trail Making Test B; Verbal fluency was assessed through digit span; language was assessed through the vocabulary subset of the Wechsler Adult Intelligence Scale III; finally, processing speeds and attention were assessed
through a forward digit span test. Depression was measured on the 17 Hamilton Depression Rating Scale. The study found no difference in overall cognitive scores from before and after implantation. In addition, researchers found significant improvement in the Hamilton Depression Rating Scale, demonstrating that DBS of the subcallosal cingulate gyrus is an effective treatment for depression. Executive functioning and memory did not decrease after surgery and scores on the Hamilton Depression Rating Scale improved therefore, these results support the use of deep brain stimulation of the subcallosal cingulate gyrus.

DBS is administered because researchers have hypothesized that deep brain stimulation of certain regions of the brain will lead to a reduction in negative-self bias, which is a cognitive symptom of MDD. Monoamine antidepressant treatment causes changes in mood which leads to changes in emotional biases however, it takes time for antidepressants to reduce negative cognitive bias. Emotional processing occurs in the network of the brain which involves the medial prefrontal cortex and the subcallosal cingulate gyrus. Yoshimura and colleagues (2010) found that MDD patients have hyperactivity in the medial prefrontal cortex and the subcallosal cingulate gyrus when processing negative words compared to a non-depressed control group. Hilimire and colleagues (2015) conducted a study in order to assess the effects of DBS of the subcallosal cingulate gyrus on treatment resistant depression patients who have negative self-bias. Researchers assessed behavior testing and electrophysiological recording in 7 patients before treatment, one month into stimulation and 6 months into stimulation. Patients completed an emotional self-referential task in which they were presented a list of 80 adjectives, half of which were negative (e.g. unlikable, mad, moody) and half of which were positive (e.g. careful, warm, kind). The words were presented on a computer screen and patients where to indicate whether the word described them. Overall, the results show that individuals had a significant
reduction in attention to negative based words throughout the course of the study and by 6 months, patients have a significant increase in attention to positive words. The results show that DBS of the subcallosal cingulate gyrus can alter the negative self-bias schema in patients with MDD. Chio and colleagues (2015), conducted a study which had similar results. They found that when stimulation occurs, patients described “a sudden calmness”, “brightening of the room” and an “increased interest in others”. Overall, DBS causes a significant positive changes in mood, attention and sociability in patients – however, these results are not exclusive to the subcallosal cingulate gyrus and other regions of the brain such as the nucleus of accumbens is also being studied.

DBS research is also being conducted on other regions of the brain, such as the medial prefrontal cortex. Recent fMRI studies have suggested that the medial prefrontal cortex is involved in processing negative information. Yoshimura and colleagues (2010) conducted a study in order to identify whether depressed individuals display hyperactivity in the medial prefrontal cortex and the rostral anterior cingulate cortex while processing of negative words. Subjects were presented with 180 traits from Anderson’s list of trait words, half of which were negative words and half of which were positive words. Subjects were to identify whether or not the word presented pertained to them. An fMRI collected brain activity while individuals responded to the presented words. fMRI results showed that the medial prefrontal cortex and the rostral anterior cingulate cortex were more active during the processing of negative stimuli in patients with depression. The fMRI results also found no difference in activation levels of the medial prefrontal cortex and the rostral anterior cingulate cortex between depressed and healthy individuals when they were processing positive stimuli. These results support Beck’s cognitive theory that there is a negative self-bias in individuals with depression. Therefore, making the
medial prefrontal cortex and the rostral anterior cingulate cortex possible brain regions which DBS could successfully treat treatment resistant depression.

Overall, 60% of individuals with major depressive disorder are characterized as successfully responding to deep brain stimulation. Despite these results, questions regarding the most effective intensity and frequency of deep brain stimulation remains unclear. Hamani and colleagues (2010), conducted a study which compared the effects of different intensities of deep brain stimulation on depressive behavioral symptoms in rats during a forced swim test. On the first day, after swimming, rats received either continuous deep brain stimulation or sham treatment for 4 hours. The same procedure was administered on the second day followed by a second forced swim test. Rats administered with 200µA on the medial prefrontal cortex had the greatest reduction in depressive responses such as immobility time. In contrast, rats administered with sham stimulation and stimulation at 400µA on the medial prefrontal cortex continued to display depressed-like behaviors such as immobility. These results provide further evidence that deep brain stimulation of the medial prefrontal cortex is effective treatment for depression, however stimulation must be administered at an effective intensity.

Deep brain stimulation of the medial prefrontal cortex has shown to successfully treat depression however, little is known about the underlying neurobiological mechanisms of DBS on the medial prefrontal cortex and specifically how it alters brain regions or chemicals related to depression. The nucleus of accumbens is located in the prefrontal cortex and is thought to control reward, laughter, pleasure and fear – all of which are affected in individuals with depression. The nucleus of accumbens controls the release of dopamine to areas of the brain such as the medial prefrontal cortex. It is known the medial prefrontal cortex monoamine activity is altered in patients with depression. Therefore, in order to mediate monoamine activity, researchers have
suggested DBS of the nucleus of accumbens as a possible treatment for treatment resistant depression. Dijk and colleagues (2012) conducted a study in order to assess the effect of DBS of the nucleus of accumbens and monoaminergic neurotransmitter levels in the medial prefrontal cortex. Researchers implanted electrodes on the nucleus of accumbens of rats while dopamine, serotonin and norepinephrine levels of the medial prefrontal cortex were measured through in vivo microdialysis. Baseline for monoamine levels were defined as the average of the samples taken before stimulation. During the 2 stimulation days, microdialysis samples were collected every 15 minutes. Compared to baseline, results showed that DBS of the nucleus of accumbens caused a significant increase of dopamine by 177% and serotonin by 127% in the medial prefrontal cortex. These results provide evidence that DBS of the nucleus of accumbens increases monoamine levels in the prefrontal cortex, similar to the effects of SSRI drugs, and provide a possible treatment for patients with treatment resistant depression.

Researchers now believed that focusing treatment on regions of the brain specifically related to depression will increase response rates in individuals with treatment resistant depression. The nucleus of accumbens is thought to be the control center of the reward system which is often impaired in individuals with depression. An impaired reward system leads to anhedonia, the inability to experience pleasure; a common behavioral symptom of major depressive disorder. Schlaepfer & colleagues (2008) assessed deep brain stimulation in patients who were extremely treatment resistant and failed to respond to pharmacotherapy, psychotherapy and electroconvulsive therapy. Researchers bilaterally stimulated the nucleus of accumbens while assessing depression. Clinical ratings of depression were measured through both the Hamilton Depression Rating Scale (HDRS) and the Montgomery and Asberg Depression Rating Scale (MADRS). Baseline HDRS score was 33.7 and baseline MADRS scale was 35.7. After
one week of stimulation of the nucleus of accumbens scores significantly decreased to 19.7 and 24.7. Similarly, after the first week without deep brain stimulation scores again increased to 29.3 and 33.3. Dopamine levels increase in the nucleus of accumbens after deep brain stimulation, thus restoring dopamine levels to a relatively standard amount, similar to levels in a healthy individual. These ratings demonstrate that deep brain stimulation of the nucleus of accumbens provides a quick and effective treatment for depression however, stimulation must remain in order to for individuals to continue experiencing a decrease in symptoms.

Deep brain stimulation is an up and coming current treatment for patients with treatment resistant depression who do not respond successfully to antidepressant medication. Although information is lacking, the studies that have been conducted yield promising results and DBS has not shown signs of impairment of executive cognitive function and memory. The three regions that have responded most effectively to DBS are the subcallosal cingulate, medial prefrontal cortex and the nucleus of accumbens. The subcallosal cingulate and the prefrontal cortex (where the nucleus of accumbens and the medial prefrontal cortex are located) are both related to processing of emotional stimuli and have been found to be significantly active when depressed individuals view negative stimuli. Overall, deep brain stimulation has been found to regulate monoaminergic neurotransmitter levels in the medial prefrontal cortex and helps eliminate the negative processing bias found in patients with depression.

**Discussion**

The purpose of the current literature review was to discuss the possible etiologies of major depressive disorder as well as the pharmacological and deep brain stimulation treatment options for individuals. Although major depressive disorder impacts millions on lives every year the disease is often pushed under the rug due to the negative connotation associated with the
diagnosis. The reality is that 17% of the population will experience major depressive disorder at some point in their lifetime. Individuals experiencing the symptoms often fail to seek help or acknowledge the problem at hand because they feel as though they are a burden or the brought the disease on themselves. However, this is not the case.

There are numerous etiologies for major depressive disorder, too many to identify a single causal factor. However, a common theme amongst individuals with depression is stress. It is reasonable to assume that any individual can suffer from depression and depressive symptoms if they are exposed to a significant amount of stress. In comparison, any individual can develop a cold if they are exposed to a significant amount of germs. However, susceptibility to the illness depends on exposure to certain germs. A cold will generally subside after proper treatment and avoidance of germs. However, repeated exposure and lack of proper treatment can cause an individual to become increasingly ill. Similarly, with proper treatment, stress normally subsides after one exposure, however individuals who experience repeated stress are more susceptible to becoming increasingly ill. After repeated exposure to stress, individuals may develop a weaker capacity for tolerating or successfully responding to stress which can lead to the development of depressive symptoms. An increased response to stress and reduction of neuroplasticity are reciprocally connected with the monoaminergic systems which can lead to alteration in the neurocircuitry of the brain and impair an individual’s ability to respond successfully to stimuli.

After severe stress causes alterations in the neurocircuitry of the brain, the next step in treatment is to identify the proper antidepressant. Overall, antidepressants essentially work to reestablish the neurocircuitry imbalance in the brain in order for individuals to function properly. Individuals who are experiencing depression for the first time will typically be administered an SSRI or SNRI antidepressant. However, similarly to the fact that not all cold remedies work for
each and every individual, not all individuals respond effectively to antidepressants. If an individual fails to respond to SSRI or SNRIs or experiences negative symptoms then they will be administered atypical drugs or MOAIs.

Similar to a cold, major depressive disorder manifests itself differently in each individual. Colds can cause people to cough, while others develop a fever while some just have a runny nose for a week. Depression can cause individuals some individuals to develop feelings of worthlessness while others refuse to leave their beds for days. Treatment of major depressive disorder results from the severity of the illness. If symptoms continue to persist and treatment is ineffective then individuals will be administered the alternative treatment of deep brain stimulation. Deep brain stimulation involves implanting electrodes into the brain to deliver adjustable electrical pulses to specific areas. Patients administered deep brain stimulation are normally deemed treatment resistant, meaning they have a history of severe depression that has failed to respond to typical treatment methods. Severe stress alters the neurocircutry of the brain therefore the idea behind deep brain stimulation is that the electrical impulses will provide circuitry support and enable that area of the brain the function properly. Enabling an individual to respond effectively to stress.

In comparison to colds, major depressive disorder can occur in any individual. Some individuals have a stronger immune system and have the ability to fight off colds quickly and effectively while others are prone to catching colds. Similarly, some individuals have the ability to shake off stress and keep working hard while others let stress reside in every inch of their being, so much so that is alters the neurochemistry of the brain and how they respond to future stressors.
Prior to writing this literature review I was unaware of the significant role that stress can play on the body. If stress is not taken seriously it can take a serious toll on an individual’s mental well-being and in severe cases lead to impairments such as depression. Individuals who are experiencing symptoms of depression need to know that treatment can be as easy as taking an oral pill once a day; rather than allowing the depressed feelings to snowball into a disaster such as a suicide attempt. If individuals fail to adhere to pharmacological treatments there are other safe and effective alternatives such as deep brain stimulation.
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