Successful Therapy for Major Depressive Disorder

Abstract

This critical literature review examines the neural mechanisms that are involved in successful treatment of major depressive disorder (MDD). MDD is a disorder that has become a relatively prevalent disorder in United States. MDD can cause drastic impairments to the lives of those that are diagnosed with it due to the cognitive impairments associated with MDD. The cognitive impairments, specifically cognitive dysfunction, can lead to suicidal thoughts, which makes MDD a disorder that needs to be taken seriously. The purpose of this literature review is to examine pharmacological, behavioral, and complementary and alternative medicines (CAMs) on their efficacy in safely treating patients with MDD.
Individuals from all walks of life experience states of depression or depressive episodes that vary in severity. Some individuals experience depressive episodes and are able to continue with their daily routines, while others experience depressive episodes and it causes impairment in their daily functions. These impairments are associated with symptoms of major depressive disorder (MDD). MDD is a mood disorder that is marked by the symptoms of feeling sad, guilty, remorseful, and worthlessness. Anhedonia, which is a lack of pleasure from previously rewarding stimuli, is one of the key symptoms of MDD. Suicidal thoughts, fatigue / lethargy, sleep / appetite change, psychomotor retardation / agitation, and impaired cognition are also common symptoms of MDD.

There are biological, psychological, and social causes that are associated with MDD. Twin studies have shown that MDD is a heritable disease. One of the prominent biological deficiencies of MDD is the low concentration level of serotonin (5-HT) in relation to other neurotransmitters like dopamine (DA), norepinephrine (NE), and epinephrine (EPI). Deficiencies in concentration levels of norepinephrine have also been associated with MDD. The raphe nucleus is the main supplier of 5-HT. Serotonin is synthesized from the amino acid tryptophan, which occurs in two main steps. The first step occurs as tryptophan is transformed into 5-hydroxytryptophan, when it adds a hydroxyl group. The second step occurs as 5-hydroxytryptophan is transformed into 5-hydroxytryptamine (serotonin 5-HT), when the enzyme aromatic-L-amino acid decarboxylase cleaves a carboxyl group from 5-hydroxytryptophan. When 5-HT is released from the raphe nucleus from the presynaptic terminal into the extracellular fluid, it binds to receptors from the post-synaptic terminal or it is metabolized by the enzyme monoamine oxidase (MAO), and then reuptake occurs and the metabolite 5-hydroxyindoleacetic acid (5-HIAA) is released.
The main psychological causes of depression are cognitive errors, where the individual has an arbitrary interference that causes the individual to focus on negative stimulus, and overgeneralization, where the individual produces a negative blame-scheme and perceives events to be extremely negative. Learned helplessness and lack of identity / purpose have also been associated with causes of MDD. The learned helplessness theory states that individuals become anxious and depressed when they decide that they have no control over the stress in their lives. Lack of identity / purpose refers to individual feeling that life is meaningless and there is a lack of unconditional positive regard. Social causes that have been associated with MDD are interpersonal problems and poor social support. These social causes can potentially lead to an inability to form or use appropriate coping methods during a depressive episode occurs.

Studies have shown that there are potential gender differences that effect individual’s susceptibility to MDD (Jovanovic et al., 2007). Men tend to have high 5-HT concentration levels, lower serotonin receptors (5-HTr), and high levels of serotonin transporters (5-HTT); thus, causing males to have more neurotransmitters, less binding of serotonin to receptors, and more reuptake of 5-HT (Jovanovic et al., 2007). Women tend to have low 5-HT, high 5-HTr, and low 5-HTT; thus, causing females to have less neurotransmitters, more binding of serotonin to receptors, and less reuptake of 5-HT (Jovanovic et al., 2007). These differences cause men to be less sensitive than women to low concentration levels of serotonin. Men are able to more easily compensate low levels of 5-HT by increasing 5-HTr and decreasing 5-HTT to compensate for low 5-HT. It is more difficult for women to compensate low levels of 5-HT because they have high levels of 5-HTr and low levels of 5-HTT. High levels of 5-HTr causes more binding of receptors and low levels of 5-HTT causes less reuptake of serotonin; thus, women are more sensitive to low neurotransmitter concentration levels (Jovanovic et al., 2007). Women are more
susceptible to depression due to a lower baseline of 5-HT and higher sensitivity to decreased levels of serotonin (Jovanovic et al., 2007).

Studies have also shown that these differences in response rates to depression are attributable to hormone differences amongst genders (Hines et al., 2006). Hines et al. (2007), with the use of a rat animal model, performed a study showing that rat females with the human gene of type VII adenylyl cyclase (ADCY7) produced higher rates of depression, when compared to male rats with the human gene ADCY7, which showed no increase in rate of depression. The rates of depression were based on two behavioral depression tests: a forced swim test and a tail suspension test. The study suggests that these sex differences are associated with the difference in hormone differences. Hormone differences have been associated with differences in response rates in regards to different neurotransmitters that are related to depression in regards to stress like oxytocin (Taylor, 2006). Taylor (2006) performed a study analyzing the differences in stress-responses in regards to different levels of oxytocin between males and females relative to their hormonal differences. The study suggests that estrogen may enhance the overall effects of oxytocin within the body.

Depression occurs during childhood and adulthood. Childhood and adulthood depression have shown similarities in behavioral symptoms, such as exhibiting sadness, crying, hopelessness, low self-worth, sleep and appetite problems, and lethargy. They differ on behavioral problems and methods of dealing with depression, such as clinging and delinquency. These differences may occur in regards to differences in social structures present for children and adults and also in regards to severity of punishment in response to behavioral problems. The National Institute for Mental Health in 2013 estimated that 10.7% of adolescents from 12-17 years of age within the US experienced at least one major depressive episode; in comparison to
6.7% of adults ages 18 or older within the US experienced at least one major depressive disorder (National Institute for Mental Health, 2013). The difference in prevalence may potentially be caused by a stronger more concrete social support system developed during adulthood and less stable more fluid social support system developed during childhood.

MDD is a prevalent disorder that affects individuals of all ages. The purpose of this literature review is to examine the most effective method to treat the symptoms of MDD, in regards to regulating and improving the neural mechanisms that are impaired within patients diagnosed with MDD. Studies on the efficacy of pharmacological, behavioral, and homeopathic forms of treatment are used to support each method of treatment to ascertain the most effective way to treat MDD.

**Pharmacological Treatment**

Pharmacological methods have been used to treat the symptoms of MDD. Antidepressants have shown to be an effect means to treating patients diagnosed with MDD. Tricyclic antidepressants like imipramine and tofranil work to block the reuptake of 5-HT and catecholamines (dopamine, norepinephrine, and epinephrine) by the presynaptic terminal, which causes 5-HT and catecholamines to be released and present longer in the extracellular fluid. Tricyclics act on many neurotransmitters, which causes additional effects like dizziness, drowsiness, blurred vision, rapid heart rate, dry mouth, and excessive sweating. Other cons to tricyclic antidepressants are that they have been associated with weight gain and sexual dysfunction, which suggests that the use of tricyclic antidepressants to treat MDD could potentially produce side effects that are worse that the initial disorder.

Monoamine oxidase inhibitor (MAOIs) antidepressants like phenelzine work to block the enzyme that breaks down and metabolizes 5-HT and catecholamine, which allows 5-HT and
catecholamines to be released and present longer in the extracellular fluid. Allowing the
neurotransmitters to be available for repackaging in the vesicle; thus, causing an increase in the
neurotransmitters release. Similar to tricyclic antidepressants, MAOIs have an effect on multiple
neurotransmitters, which causes it to have side effects, such as dizziness, drowsiness, blurred
vision, rapid heart rate, dry mouth, and excessive sweating. Another con to using MAOIs to treat
MDD are dietary restrictions that yield the individual unable to eat foods or drinks with
tyramine, which is an amino acid associated with the regulation of blood pressure. Foods and
beverages that contain high levels of tyramine produce an interaction with MAOIs that can lead
to dangerous levels of high blood pressure, which may cause cardiovascular complications
(Shulman, Herrmann, and Walker, 2013).

Selective serotonin receptor inhibitor (SSRIs) antidepressants like fluoxetine and prozac
work to block reuptake of 5-HT by the presynaptic terminal, which allows 5-HT to be present
longer within the extracellular fluid when released. SSRIs are more commonly prescribed to
patients with MDD because they have milder side effects due to the fact that they only affect one
neurotransmitter.

This section presents studies measuring the overall efficacy of pharmacological treatment for
MDD, while also examining different types of pharmacological therapy, novel drugs with
antidepressant-like effects, and differences in efficacy of different classifications of
antidepressants.

Combination strategies have been clinically implemented to increase the efficacy of
pharmalogical treatment for patients with MDD. Fluoxetine and olanzapine have been used in
combination to treat the symptoms of MDD, and have been approved for treatment resistant
depression by the FDA (Rizvi, 2013). Olanzapine is an atypical antipsychotic that works by
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blocking the D2 receptors, which allows dopamine to stay active longer (Seeman, 2002). Patients diagnosed with MDD show symptoms of anhedonia, which has shown a strong connection to emotional processing. This irregularity in reward-based phenomenology can potentially be a baseline predictor for pharmacological treatment outcomes in regards to reward function acting as a mediator of antidepressant response both at the behavioral and neural level. Rizvi et al. (2013) performed a study to determine if brain activation relative to negative and positive images during baseline could be a predictor for treatment outcome in response to a 6-week treatment of fluoxetine and olanzapine in patients diagnosed with MDD. The study was performed by measuring brain activity at baseline and week 1 of treatment with an fMRI, while being shown pictures from the International Affective Picture Rating Scale. The Hamilton Rating Scale for Depression (t-17) was used to measure the efficacy of the treatment in relation to baseline and the 6-week trial of the drugs fluoxetine and olanzapine. The results showed that individuals with MDD had higher baseline premotor activity while viewing negative images, which the higher baseline was predictive of a greater percent change on the HAMD-17 and improvement in negative disposition and behavioral drive with the combination therapy. The findings from this study show that combination treatment with fluoxetine and olanzapine show similar predictive response rates with biomarkers (posterior cingulate cortex, anterior insula and premotor cortex), in relations to monotherapeutic SSRI treatment. This study shows the efficacy of using the combination of fluoxetine and olanzapine to treat symptoms of MDD, along with potentially using fMRIs to identify biomarkers that can predetermine the most responsive drug for an individual diagnosed with MDD.

Some of the clinically prescribed antidepressants have been found to have adverse side effects on the individuals taking them, such as gastrointestinal symptoms, agitation, sleep
disturbance, and sexual dysfunction (Fava et al., 2012). The adverse side effects, regardless of the efficacy of the antidepressants on the symptoms of MDD, can lead to problems with treatment compliance with the individual, especially if one of the side effects is sexual dysfunction. Fava et al. (2012) conducted a study to find other forms of pharmacological medication to treat the symptoms of MDD. The drugs buspirone, a receptor agonist and a presynaptic dopamine agonist and partial alpha receptor antagonist, and melatonin-SR, which allowed for a slow release of melatonin, when used in monotherapy showed little to no effect on the treatment of the symptoms of MDD, but when used in combination with the correct combination ratio are effective in treating the symptoms of MDD with minimal adverse side effects. Brain Inc. (BCI), using an in vitro and in vivo neurogenesis platform, has been able to study effects of drugs and identify potentially new antidepressants (Fava et al., 2013). BCI discovered that low doses of buspirone (15mg) in combination with melatonin-SR within neurogenesis platform assays produced antidepressant-like effects within the assays, which was shown through increased hippocampal neurogenesis produced using the combination therapy. In relations to the findings from BCI, Fava et al. (2012) conducted their study to measure the efficacy of the drugs on individuals diagnosed with MDD. This six-week experiment was a double bind, randomized, placebo study with three groups: drug combination group (15 mg buspirone IR and 3 mg melatonin-SR), monotherapy group (15 mg buspirone), and matching placebo group. The results of this study showed that low doses of buspirone in combination with melatonin led to a significant antidepressant-like effect that was greater than the placebo or buspirone monotherapy groups. This effect was measured through a multiple diagnostic measurement test of MDD (Clinical Global Impression of Severity and Improvement, Inventory of Depressive Symptomatology) used to measure MDD symptoms. These preliminary findings
on the efficacy of this new combination of drugs can lead to future studies with more participants in hopes of more robust effects. This study shows that researchers are searching for drugs that effectively treat MDD negative side effects.

Twenty percent of patients that have an episode of MDD meet the criteria for psychotic depression, which is a subtype of MDD that is paired with some form of psychosis (hallucinations, delusions, or being out of touch with reality) (Wijkstra et al., 2009). Wijkstra, J. et al. (2009) conducted a study to measure response and remission rates, along with tolerability, of pharmacological treatment of psychotic depression with either monotherapy or combination therapy. Remission refers to patient no longer exhibiting symptoms of the disorder. Their study used the antidepressant venlafaxine, a serotonin-norepinephrine reuptake inhibitor, and the antipsychotic quetiapine, an atypical antipsychotic, with one group receiving only the antidepressant and another group receiving the antidepressant in combination with the antipsychotic. The results from the study showed that there were no significant differences between the groups, but the combination group had a slightly higher remission rate than the monotherapy group. The combination of the antidepressant and the antipsychotic drugs caused parallel effects on the depressive and psychotic symptoms, meaning that the individuals were free of both depressive and psychotic symptoms. While the drugs did cause the individuals to have a slight weight gain, they were effective in treating the symptoms and lowering relapse rates and increasing remission rates from 59.3% to 86.8%; thus, the rates of patients not showing symptoms increased, while the rate of these patients going back to showing these symptoms after treatment decreased. This study gives insight into the efficacy of combination drugs in regards to remission and relapse rates for individuals diagnosed with depression.
From the previous articles, it is easy to discern the effectiveness of pharmacological treatment of MDD, whether it is through monotherapy or a combination of drugs. Depression has also come to be associated with platelet activity because platelets are able to take up, store and metabolize 5-HT; thus, even though serotonin is a weak platelet agonist low concentrations of it can lead to enhanced platelet aggregation (Moreno et al., 2012). Platelet aggregation derives from the increased expression of 5-HT\textsubscript{2} receptors that leads to the increase in concentration of intra-cellular calcium (Moreno, et al., 2012). Increased concentrations of intra-cellular calcium are often associated with exocytosis. Nitric oxide (NO) helps to regulate platelets and more importantly inhibits platelet aggregation, but the role of NO with the onset of MDD has not been determined. Moreno et al. (2012) performed a study to examine the levels of NO, in regards to platelet mitochondrial membrane potential and P-selectin, of individuals that have been diagnosed with MDD, but have not used pharmacological treatment. P-selectin has been a proven indictor of platelet activity. The study measured the overall concentrations of serotonin and tryptophan in relation to platelet activity. Measuring platelet activity is a model to examine the serotonin mechanism within patients that MDD because platelets play a key role in the synthesis, storage, and uptake of serotonin. The results showed that there was an overall lower concentration of serotonin and tryptophan for the patients with MDD, but there was no significant difference in serotonin concentrations within the platelets between the healthy group and untreated MDD group. There was higher P-selectin expression within the MDD untreated group than the healthy group, which shows that there is increased platelet activation for the MDD group. The increased platelet activation is associated with platelet aggregation. The results suggest that there is a potential change in the functionality of the platelets for untreated patients with MDD, which is shown through the increased expression of P-selectin or increased platelet
activity. The study presented by Moreno et al. (2012) gives insight into the potential etiology of MDD, while also showing the effects of not using pharmacological means of treatment for MDD.

Individuals diagnosed with MDD have reported cognitive impairments. These cognitive impairments have been detected in attention, mental processing speed and motor performance, memory, working memory, and executive functions, including allocation of attentional resources, inhibitory control, fluency, planning, and self monitoring (Herrera-Guzmán et al., 2009). Cognitive functions do improve within remission after pharmacological treatment, but deficits in verbal memory and verbal fluency are still present. Herrera-Guzmán et al. (2009) presented a study to examine the effect of SSRIs and dual serotonergic-noradrenergic reuptake inhibitors (SNRIs) on cognitive impairments for individuals with MDD. The study also measured the cognitive functioning after treatment with SSRIs or SNRIs in comparison to unmedicated patients during remission, while also examining if there were any differences in cognitive performance during remission between the two types of antidepressants. The results from this study show that there is continued cognitive dysfunction during remission in regards to verbal and visual episodic memory, sustained attention, mnemonic and strategic aspects of working memory, and planning. This cognitive dysfunction was also present 24 weeks after antidepressant withdrawal and the unmedicated groups, which suggests that within this period of time there is cognitive dysfunction that extends beyond the clinical symptoms (Herrera-Guzmán et al., 2009). Also, the results show that patients treated with SSRIs showed more memory impairment than those treated with SNRIs, which shows that SSRIs might not be as effective and that there are potential side effects. The study presented gives insight to the cognitive deficits
that are associated with MDD, while also examining efficacy of different types of antidepressants in treating cognitive deficits in patients with MDD.

The neuropeptide oxytocin is known to be influential in reducing anxiety and promote social bonding because of its effects on the hypothalamopituitary adrenal (HPA) axis. Oxytocin is synthesized in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus, where it is released and distributed within the brain through oxytocinergic pathways and oxytocin receptors (Keating, Dawood, Barton, Lambert, & Tilbrook, 2013). Oxytocin is more prevalent within areas of the brain that relate to stress-anxiety and social responses. Studies have shown that oxytocin, within humans, increased and improved social communication. Oxytocin has also been shown to reduce anxiety and mitigate activity within the HPA-axis. Individuals that have been diagnosed with MDD report difficulties with interpersonal relationships and feelings of social isolation. Along with self-reports, up to 60% of individuals diagnosed with MDD have elevated levels of activity within the HPA-axis. Keating et al. (2013) performed a study measuring the effects of SSRIs on oxytocin and cortisol levels before and after treatment. SSRIs have been a proven effective form of pharmacological treatment for the symptoms of MDD. The study was performed to analyze the potential relationship between oxytocin and cortisol concentrations relative to symptoms of MDD. The study was performed by sampling the arterial blood from patients diagnosed with MDD before and after the 12-week treatment of the SSRI fluoxetine. The results did not shown any significant difference between oxytocin or cortisol concentration in relation to before the SSRI treatment was administered. The study shows the efficacy of SSRIs on the symptoms of MDD, and shows that the physiological response to stress does not seem to be a major factor in the symptoms of MDD. The study also highlights the relationship between oxytocin and SSRIs with regards to MDD and reducing
anxiety / stress, suggesting that SSRI’s are effective in lowering stress levels related to depressive episodes.

The pharmacological approach to the treatment of symptoms for MDD has been proven successful, especially with comparison to lack of pharmacological treatment. Monotherapy has been a successful form of treatment, but combination therapy of antidepressants has shown to be more effective in regards to efficacy and the lack of significantly negative side effects. Combination therapy allows for lower dosage of antidepressants, while also helping to increase treatment compliance. SNRIs have been shown to be a more effective antidepressant than SSRIs on treating cognitive symptoms of MDD. Overall, the studies on pharmacological approach to treatment for symptoms of MDD have shown ways to improve the efficacy of antidepressants through combination therapy, more effective novel antidepressants that lack negative side effects, and the use of biomarkers to assign the most effective antidepressants for individuals.

Pharmacological treatment is shown to be an effective means of treating MDD not only due to the effects of treatment, but it is also a relatively simple way to treat depression. One is able to simply take a pill take care of their symptoms, without having to going through any other complicated means of treatment. Pharmacological treatment of MDD is a time efficient way to treat the symptom because the individual can take the antidepressant when they wake up and not suffer any symptoms of MDD for the rest of the day. The ease of treatment makes pharmacological treatment an effect and attractive means of treating the symptoms associated with MDD.

The studies presented show that pharmacological treatment is successful in treating the symptoms associated with MDD, along with showing the efforts of researchers to find more effective novel drugs or drug combinations to treat MDD while minimizing side effects.
**Behavioral Treatment**

Behavioral treatment attributes MDD as a disorder that occurs due to learned and unlearned responses, where treatment is specific to the behavior. The client’s report of MDD symptoms and episodes are valid and the goal of treatment is to change the maladaptive behavior and substitute it with adaptive behavior. Behavioral treatment studies relationship of cues / contingencies and reinforcement or lack of reinforcement, focused on changing cues / contingencies and to change behavior. Behavioral therapy has been proven to endogenously increase the production of 5-HT, which is shown through the comparison of behavioral treatment paired with placebos to pharmacological treatment.

Cognitive-Behavior Therapy (CBT) is a type of behavioral treatment that focuses on changing the thoughts of the individual diagnosed with MDD to treat the behavioral symptoms MDD. CBT focuses on irrational thoughts of individuals with MDD where the individual produces a negative blame-scheme and perceives events to be extremely negative. The main goal of CBT is to substitute rational thoughts for irrational thoughts. In regards to one of the main symptoms anhedonia, CBT works to establish a stronger reward system by disrupting the cognitive irrational thought process that occur with learned helplessness and lack of meaningfulness / purpose. CBT focuses on changing the dysfunctional attitude present in individuals diagnosed with MDD and substituting it with a more functional attitude.

Psychotherapy, or therapy, is another type of behavior treatment that focuses on the individual working out problems that were established earlier in life. The main assumption for psychotherapy is that the disorder is caused by childhood problems and unconscious conflicts. The therapist acts anonymous, abstinent, and ambivalent when engaged with client that is diagnosed with MDD, to allow the client to resolve the conflict internally on his or her own. Free
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association, dream interpretation, and transference are techniques employed by therapists. Free association allows the client to freely speak his or her mind without limits or constraints from the therapist that might influence the client’s thoughts. Dream interpretations allow the therapist to analyze the dreams of the client. Transference occurs when the patient regards the therapist as his or relative or friend and the patient enacts the relationship with the therapist. Each of these methods allows the client to give an unbiased report of childhood problems or unconscious conflicts, allowing the client to resolve these childhood problems or unconscious conflicts on their own. Problems with psychotherapy are that it requires a lot of time and interaction between the client and therapist because the therapist has to gain the client’s trust to allow the client to open up and freely speak about his or her problems. The prolonged time spent between the client and therapist and overall interaction can lead to the client becoming too dependent on the therapist and becoming impressionable, or countertransference may occur, where the therapist develops personal feelings for the client.

This section presents studies measuring the overall efficacy of behavioral treatment for MDD. The section examines MDD in regards to the neurological biology of learned helplessness and conditioned defeat, and the neural effects and long-term efficacy of behavioral treatment. It also focuses on the cognitive mediation of depression and neural effects of psychotherapy.

Early or late exposure to highly stressful stressors has been proven to be a key factor in the onset of MDD, but the influence of the stressor’s characteristics have not been clearly defined (Hammack, Cooper, & Lezak, 2010). Studies have shown that exposure to traumatic events can increase the risk for MDD, but have also shown that exposure to negative events that are not highly traumatic can lead to an increased risk of MDD as well. Rat animal models have been used to demonstrate depression because of their behavioral responses to stressful stimuli that
mimic that of patients diagnosed with MDD. Hammack, Cooper, and Lezak (2010) conducted a study to measure the neurological effects of learned helplessness and conditioned defeat within an animal model in relation to MDD. The study produced an animal model of learned helplessness by exposing rats to inescapable, but not escapable, tail shocks, which the uncontrollable nature of the shocks increased fear / anxiety-like behavior that was similar to humans with learned helplessness. This was observed through behavioral responses from the rats that were similar to humans with learned helplessness, such as reductions in fight / flight responses, disrupted sleep patterns, disrupted food and water intake, and the subsequent failure to learn to escape aversive stimuli in subsequent tasks where escape was possible (Hammack et al., 2010). Conditioned defeat, which models social defeat for humans, is a stressor that produces depression-like behaviors, such as loss of species-typical territorial aggression and increased submissive and defensive behavior in subsequent social encounters with smaller non-aggressive intruders. The animal model for conditioned defeat is similar to the model used for learned helplessness, but the behavioral markers of conditioned defeat in rats is a reduction in social investigation with juvenile conspecifics (Hammack et al., 2010). A major difference in the two models is that stressor controllability for the learned helplessness model is critical, but the conditioned behavior model is still produced even if the rat is able to escape from the aggressor during training. The results showed that both the learned helplessness and conditioned defeat group high levels of 5-HT activity within the dorsal raphe nucleus played a key role in the control of learned helplessness and conditioned defeat, which is suggested through the differences in levels of 5-HT. The results also highlighted the basolateral amygdala (BLA), central nucleus of the amygdala (CeA), and bed nucleus of the stria terminals (BNST) as having roles in the regulation of acquisition / expression of the behaviors associated with learned
helplessness and conditioned defeat. The study presents insight into the neurobiology associated
with learned helplessness and conditioned defeat and the critical areas involved with learned
helplessness and conditioned defeat, while highlighting a potential interaction between the dorsal
raphe nucleus and emotion-related regions of the brain on the acquisition / expression of learned
helplessness and conditioned defeat.

Individuals can be diagnosed with MDD as co-occurring disorders with another disorders as
a comorbid disorder. Comorbid disorders occur when two disorders have similar symptoms or
symptoms / causes of the disorders are linked to each disorder. Special behavior therapy methods
for treatment can be created to help specific comorbid disorders. Behavioral and motivational
enhancement therapy (MET) has been used to specifically treat the symptoms of comorbid MDD
/ alcohol use disorder (AUD) because the symptoms of AUD are potentially linked to the causes
of MDD. The motivational enhancement therapy is used to facilitate an individual’s increased
engagement in therapy and motivation to make changes regarding substance use and high risk-
behavior. Cornelius et al. (2011) presented a study to compare the efficacy of behavioral therapy
and motivational enhancement on adolescents with comorbid MDD / AUD to pharmacological
treatment. The study performed a longitudinal study to measure the longevity of efficacy for
CBT / MET during a two-year follow-up where individuals were given naturalistic treatment or
CBT / MET either with the administration of the SSRI fluoxetine or a placebo. The results
showed that the CBT / MET (both SSRI & placebo) was more effective in treating the comorbid
symptoms for MDD / AUD during the two-year follow up, in comparison to the placebo group.
When comparing the fluoxetine and placebo groups, during the two-year follow up, within the
CBT / MET there was not a significant difference between the two groups in efficacy of treating
the comorbid symptoms for MDD / AUD. This study shows that CBT / MET have potential
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long-term efficacy, while also showing that CBT / MET has similar efficacy when compared to pharmacological treatment.

Dysfunctional attitudes towards stressful events in life are characteristics of depressive episodes experienced by individuals diagnosed with MDD. This dysfunctional attitude can be attributed to the development of a negative schema based on loss, failure, and abandonment in response to negative life events experienced by the individual. Studies have found that dysfunctional thinking during a depressive episode is associated with greater 5-HT receptor binding potential within the specific regions of the brain, such as the anterior cingulate, prefrontal regions, thalamus, caudate and putamen (Sankar et al., 2014). Sankar et al. (2014) presented a study to identify the neural effects of CBT on dysfunctional attitudes in depression. The study used the dysfunctional attitude scale (DAS) to measure the efficacy of CBT on MDD, while an fMRI was used to measure brain activity present during treatment. The results show that CBT normalized the responses to DAS statements for individuals diagnosed with MDD, which shows similar results as patients treated with antidepressants. In comparison to the healthy group, individuals diagnosed with MDD that were treated with CBT showed greater activation in the left hippocampal region, inferior parietal lobe and precuneus, which was measured using fMRI. This study gives insight into the brain regions attributed to CBT, in regards to dysfunctional attitudes, which can be used to further understand the neural mechanisms involved with behavioral treatment.

Quilty, McBride, and Bagby (2008) performed a meta-analysis to measure the overall effectiveness of using the cognitive meditational model of CBT for depression. The analysis was conducted to evaluate the role of dysfunctional attitude as a mediator of the symptoms of MDD. There were two models that were presented as explanations of dysfunction attitude being the
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mediator of MDD: the cognitive meditational model, where CBT focuses on the changing dysfunctional attitude to treat depression; and the complication model, where CBT focuses on changing depression to cause a change in dysfunctional attitude. Results from individuals diagnosed with MDD that were treated with CBT, intrapersonal therapy (IPT), and pharmacological therapy (PHT), with CBT compared to IPT and PHT. The results were based on individual’s results from the HAMD-17, Beck Depression Test Inventory-II, and DAS prior to and after treatment. The results from the analysis when CBT was compared to IPT, showed CBT with greater dysfunctional attitude change. Greater dysfunctional attitude change was paired with a greater reduction in depressive symptoms. When CBT was compared to PHT, PHT showed a greater depressive symptom reduction, and greater depressive symptom reduction was paired with greater depressive attitude change. This study shows that the dysfunctional attitude may play a causal role in depression for CBT, but not PHT (SSRIs) because PHT may cause the complete deactivation of dysfunctional thinking.

Karlsson et al. (2010) conducted a study to identify the molecular effects of psychotherapy in comparison to the SSRI fluoxetine, while measuring alterations in receptor 5-HT binding potentials using positron emission tomography (PET) scanning. One group of individuals diagnosed with MDD received brief psychotherapy and the other group received the SSRI fluoxetine. The results showed an increase in 5-HT receptor binding in response to psychotherapy, while there was no change observed in patients that received the SSRI fluoxetine. Both groups did show similar symptom ratings after treatment. This study shows how molecular imaging can be used to measure the neurobiological changes produced from psychotherapy. It also gives insight into differences on how individuals respond to antidepressants and psychotherapy, while both being effective in treating the symptoms of MDD. The increase of 5-
HT receptors binding potential in response to psychotherapy can be attributed to top down modulation of the serotonin pathway in response to increased emotion regulation because psychotherapy is a method of emotional learning (Karlsson et al., 2010).

Brief Behavioral Activation Therapy for Depression (BATD) is a form of psychotherapy that can be used to treat MDD because it works to increase engagement with rewarding stimuli and reduce avoidance behaviors to combat anomalous neurobiological responses to pleasant stimuli which is associated with depression. Dichter et al. (2009) conducted a study to analyze the effects of psychotherapy on neural responses to rewards in individuals diagnosed with MDD. The study used BATD in concordance with function magnetic resonance imaging (fMRI) scans to measure neurological response changes while being presented with a Wheel of Fortune task, which was able to distinguish between reward choice selection, anticipation, and feedback of the patient. The results showed that there was a significant increase in activation of the right paracingulate gyrus, the right posterior superior temporal gyrus, and portions of the left supramarginal gyrus in response to BATD, in regards to reward selection. For reward anticipation, there was an increase in activity within the left caudate nucleus, the left cingulate gyrus, left frontal gyrus, and right insula in response to BATD. For reward feedback, there was a decrease in activation of the right caudate nucleus and the left paracingulate gyrus in response to BATD. The study shows that there is increased striatal activation during reward anticipation in response to BATD, instead of ventral striatum activation. The caudate is associated with linking rewards to behavior, reward-related decision-making, and encoding motivational feedback, while the nucleus accumbens is associated with the representation of predicted rewards (Dichter, G. et al., 2009). The wheel of fortune task requires behavioral movements, which could potentially be the cause of this contrast in the expected results of activation and the actual results. This study
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shows an overall efficacy of BATD to improve functioning of reward structures with individuals diagnosed with MDD, even if those structures are novel.

The studies presented show that the behavior approach to the treatment of symptoms for MDD has been shown to be effective and long lasting. The studies also examine the neurological changes produced from cognitive impairments associated with MDD, such as learned helplessness and conditioned defeat. Behavior therapy, with the help of placebo treatments, has also been shown to have similar effects to pharmacological effects in treating symptoms of MDD. Dysfunctional attitudes are effective and reliable measures for CBT as a mediator of depression, but it does not act as mediator for other forms of therapy like pharmacological therapy, which may be due to other effects of antidepressants on the system. Behavior therapy has been shown to produce neurological changes in the neurobiology that differs from pharmacological treatment, but they both produce similar effects.

Behavioral treatment of the symptoms of MDD are effective in treating the symptoms of MDD, but are also effective in treating the underlying cognitive deficits associated with MDD. This form of treatment is very valuable to individuals diagnosed with MDD because it allows the individuals to take control over their actions and internally solve the problem without external substances. Solving the problems with external substances can lead to overdependence on these substances that can potentially lead to overdose, and more importantly covering up the problems / causes associated with MDD instead of solving them. Behavioral treatment allows for the individuals to self-treat their symptoms of MDD, when in some instances they may not have antidepressants to take at that time. It prepares the individual to handle depressive episodes that are spontaneously triggered, which is important because one’s daily life is often unpredictable in regards to the different stimuli the individual will come in contact with from day to day.
Treating the symptoms of MDD with the behavioral treatment approach has been shown to be just as effective as pharmacological treatment, and does not have adverse side effects. It also gives the individual the ability to self-treat him/herself without dependence on a drug. Behavioral treatment is a beneficial form of treatment of MDD that is important to treating individuals MDD because it gives them confidence in themselves to conquer MDD.

**Complementary and Alternative Medicines**

Complementary and alternative medicines (CAMs) have been sought out by patients as a means to treat MDD because of the side effects and costs attributed to the orthodox forms of medication that are used to treat MDD. Some individuals seek CAMs because they do not wish to be diagnosed with MDD; therefore, they focus on the individual problems instead of attributing them to MDD, whereas individuals might see insomnia or tiredness as a single problem instead of as a symptom for MDD. Some commonly used CAMs are homeopathy and traditional Chinese medicine (TCM), in the form of acupuncture treatment.

Homeopathy is designed to provoke the body’s own defenses and self-regulatory and homeostatic responses (Reilly, 2005). Homeopathy focuses on “like” curing “like,” which refers to Hippocrates philosophy of “By similar things a disease is produced and through the application of the like is cured” (School of Homeopathy, 2015; Mantle, 2002). Homeopathic treatment is often individualized to the individual with the individual receiving diluted samples of a toxin that is diluted enough not to be toxic, but potent enough to evoke the body’s homeostatic responses (Reilly, 2005). Homeopathic treatment is based on the ideal that the body is able to heal on its own, without the use pharmacological treatments. One of the key differences with homeopathic treatment and orthodox treatment is that orthodox treatments are designed to limit, block, or mimic body reactions, but homeopathic treatment provokes the body’s own
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homeostatic responses for treatment (Reilly, 2005). Homeopathic treatment is not reported to be ineffective, but there is scientific skepticism about its efficacy, in regards to it just having a placebo effect. There are not many clinical trials of homeopathic treatment, but there are many observational studies that have found correlative evidence of homeopathic treatment being effective. Homeopathy has been reported to not produce unwanted side effects, in comparison other orthodox forms of treatment.

TCM focuses on chi, blood, and yin as the leading causes of mental / emotional problems. Chi is life energy, blood is the lubricant that nourishes the body, anchors the mind and aids the development of clear and stable thought processes, and yin reflects the passive and reflective aspects of a person (Mantle, 2002). Within TCM mind and body are seen as one, where chi, blood, and yin affect the person as a whole. TCM works to replenish deficiencies in chi, blood, and yin that are produced by mental or emotional problems using specific acupuncture points on the body or herbal remedies. Acupuncture focuses on inserting needles to specific points on the body to release or manipulate the flow of energy, or chi, through out the body. Studies have shown TCM to be an effective means for treating depressive symptoms.

This section presents studies examining the overall efficacy and safety of CAMs, specifically homeopathy and TCM, to treat the symptoms of depression in comparison to orthodox forms of treatment.

Post stroke depression (PSD) is one of the most common neuropsychiatric consequences that occurs after an individual experiences a stroke. PSD can lead to increased disability, morbidity, and mortality. Experiencing a stroke gives an individual a sense of loss of control or helplessness, which aides in triggering the onset of MDD. One third of stroke survivors are reported to have experienced major depression, along with the adverse effects on cognitive
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function, functional recovery, and survival (Qian et al., 2015). SSRIs, with fluoxetine being the most commonly prescribed SSRI, have been used to treat PSD and have been reported to have some efficacy in treating PSD. While SSRIs seem to be effective, patients taking SSRIs tend to lack ability to obtain full remission, experience relapse, functional impairment, and there are reports of increased rates of suicide (Qian et al., 2015). Traditional Chinese acupuncture is a commonly used alternative form of treatment for mental disorders and different chronic diseases within China and other parts of the world. Qian, X. et al. (2015) performed a study to evaluate the efficacy of treating patients diagnosed with PSD with traditional Chinese acupuncture, while examining potential side effects. The study divided patients diagnosed with PSD into two separate groups: group A received body acupuncture and a placebo pill, and group B received fluoxetine and minimal nontraditional acupuncture. Both groups received a placebo form of the other form of treatment to allow for accurate comparisons between groups. The groups were tested on the HAMD-17 during baseline and follow-up periods to compare the efficacy of each treatment. The results showed that overall HAMD-1 scores decreased from baseline for both groups during follow-up check-ins, but that there was no statistical difference between groups for the follow-up check-ins. Group A (acupuncture + placebo) had a quicker response time for treatment when compared to Group B (fluoxetine + minimal nontraditional acupuncture). Both groups showed adverse side effects of physical tiredness, dry mouth, sleep disturbance, and constipation, but Group B (fluoxetine + minimal nontraditional acupuncture) had more severe rates of side effects than Group A (acupuncture + placebo). This study suggests that acupuncture as an alternative form of treatment for PSD has similar rates of efficacy when compared to treatment with the SSRI fluoxetine, but with less aversive side effects and more effective response rates.
Electroacupuncture (EA) is another alternative form of treatment for depression that is similar to regular acupuncture. Electroacupuncture is the electrostimulation of the acupuncture needles that are inserted in the body at the designated chi locations. EA treatment has been reported to alleviate depressive-like behavior through the activation of the ERK-CREB pathway. The ERK-CREB pathway works through c-Jun NH2-terminal kinase (JNK), p38MAPK, and extracellular kinase (ERK), which are all mitogen-activated protein kinases (MAPKs) (Xu et al., 2015). MAPKs all regulate various cellular activities, such as proliferation, differentiation, apoptosis / survival, inflammation, and innate immunity (Xu et al., 2015). Overall, the signaling pathways for MAPKs provide the pathology of neurodegenerative and cognitive disorders found in humans (Xu et al., 2015). The ERK pathway is associated with learning, memory, and neuroplasticity (Xu et al., 2015). Xu, J. et al. (2015) performed a study to examine EA and the underlying mechanism that allows for its antidepressant-like effects when treating MDD. The study used a sucrose intake test, open field test, and forced swimming test to measure the effects of EA on induced unpredictable chronic mild stress (UMCS-induced) depression-like behavior on rats. There were four groups of seven rats: a Normal group (control), a model group, an EA group, and a sham EA group. The model, EA, and sham EA group all received chronic unpredicted mild stress (CUMS) twice a day. The EA group received EA treatment in the mornings, the sham EA group received sham EA, which consisted of setting up for EA without actual administration of EA, in the mornings, and the model group did not receive any treatment. At the conclusion of the behavioral tests a western blot analysis of the sacrificed rats was performed to measure the relative levels of each signal protein. The results showed that the model group showed a significant impairment in immobile time in comparison to the normal group, and the EA group had a significant effect on the decrease of immobile time in comparison
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to the sham EA group. The open field test showed that the model group had a significant
decrease of total distance traveled in comparison to the normal group, but there was no
significant difference in distance traveled between the EA and sham EA group. The sucrose
intake showed that the model group had a significant decrease in sucrose intake in comparison to
the normal group, and the EA group had a significant increase in sucrose intake in comparison to
the sham EA group. The western plot analysis showed that overall depression caused deficit in p-
ERK and p-p38 within the hippocampus, which the EA group showed a reversal of this effect
when compared to the other groups. This study shows that EA is effective in alleviating some of
the behavioral symptoms associated with depression, which shows EA produces similar
behavioral effects as the SSRI fluoxetine. It also presents a different pathway that is affected
through depression and how EA potentially works to alleviate or reverse the deficits on this
pathway produced from stress.

Pharmacological treatment approaches to treating symptoms of MDD run into problems with
a lack of concordance. Individuals taking tricyclic antidepressants like imipramine have a 54%
dropout rate in comparison to SSRIs like paroxetine have a 42% dropout rate which can be
associated with the negative side effects associated with the drugs, or the overall cost of the
drugs (Katz et al., 2005). Individuals tend to seek homeopathic means of treatment because of its
associated safety due to the fact that homeopathic treatment rarely shows aversive reactions.
Katz et al. (2005) conducted a pilot study to measure the feasibility of a clinical trial to examine
the efficacy of homeopathy compared to placebo and fluoxetine in the treatment of the symptoms
of MDD. Individuals diagnosed with MDD were randomized to groups (homeopathic,
pharmacological, and placebo) in a double blind study to measure the efficacy of homeopathic in
comparison to the pharmacological and placebo groups, which results were measured through
HAMD scores. The model was unable to go to fruition because out of the 31 suggested participants only 23 made it through screening, and of those 23 only 11 entered the trials, and of those 11 only six completed the study. The six that completed the study were: one that received homeopathy, two that received placebo, and three that received fluoxetine. The results showed that there were no adverse side effects to homeopathic treatment, while the group that was administered fluoxetine experienced sleep disorders and sweating side effects. These results are unable to be considered as valid because of the relatively small sample sizes of the condition groups. This study does show a potential similarity in treatment of symptoms for individuals diagnosed with MDD between the homeopathic and pharmacological treatments, but with the exception of homeopathic not producing adverse side effects.

Postnatal depression (PND) is a form of MDD that is reported to occur within 10-15% of women, which is thought to be an underestimated diagnosis because women are reluctant to self-report (Mantle, 2002). The symptoms that are associated with PND are low mood, anxiety, lack of interest and concentration, changes in sleep and appetite patterns (Mantle, 2002). Lack of sleep is often associated with having a baby, but can be noted as a key consequence to depression that might also attribute to low numbers of self-report of PND. Some mothers see conventional intervention as an intolerable means of treatment not just for reasons dealing with the potential side effects of treatment, but because of two key reasons: one, that professional health care is not appropriate and two, that mothers are unwilling to be labeled as mentally ill or unfit to care for their children (Mantle, 2002). Mantle (2002) performed a survey of complementary and alternative medicines (CAMs) to treat postnatal depression on the basis that CAMs are potentially equally beneficial treatments that patients are willing to use. Two key forms of CAMs that were focused on were homeopathy and TCM. The survey found that several remedies
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that have been used as forms of treatment for the symptoms of depression. Lycodium can be taken for fear of failure, Ignatia can be taken for insomnia and loss of appetite, and Sepia can be taken for tiredness, irritability, loss of interest, and indifference. A key finding was that homeopathic remedies could be taken in concurrence with orthodox medication. The survey also highlighted the methodology of TCM. Chi, blood, and yin are affected by one’s emotional state, which means that under this reasoning chi, blood, and yin influence the mind (Mantle, 2002). TCM describes PND as a deficiency in blood and chi, or shen, which keeps the mind sharp and alert. Acupuncture has been proven to be effective in the treating of insomnia, which is associated with depression and other emotional problems (Mantle, 2002). This survey brings to attention CAMs that have been shown to produce similar effects as orthodox methods of treatment, but more importantly have a strong safety record. CAMs can be used as methods of treatment that patients, especially in regards to mothers diagnosed with PND, are complaint with and will see through to the end.

Antidepressants have been reported to have no effect on mild or moderate depression and little effect on remission (Viksveen & Relton, 2014). As mentioned previously, antidepressants have been found to have significant side effects, along with 17-30% of patients going through relapse with depressive symptoms within 1-3 years (Viksveen & Relton, 2014). While there are multiple studies proving the efficacy of CBT, the depression trials on this method of treatment are limited, which gives CBT a relatively low level of validity due to its small effect size (Viksveen & Relton, 2014). In the United Kingdom depression is one of the key uses for homeopathic treatment, where it is publicly funded. Viksveen and Relton (2014) are performing a study to evaluate the acceptability and clinical / cost effect of homeopathic and orthodox treatment for patients diagnosed with MDD. The study is using the cohort multiple RCT
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(cmRCT) design with participants from the South Yorkshire Cohort (SYC), which is a large observational study and multiple trials facility, that self-reported long-standing depression. The evaluation is based on the individual’s overall questionnaire response in regards to self-reported levels of depression in concurrence with cost effectiveness of the treatment at 6 and 12 months, which was based on randomized groups of treatment. The individuals are offered treatment from a homeopath compared to usual care alone, where usual care for the individuals might consist of nothing or any other form of treatment. This is an ongoing study so the results have not been completely analyzed, but it shows that researchers are looking into better understanding the acceptability and effectiveness of homeopathic treatment.

Women are 1.5 to 3 times more at risk for MDD, with menopause being one of the main contributors to this increased risk for women, when compared to men. Perimenopausal period is the interval during women’s menstrual cycle when their cycle becomes irregular, which has been correlated with an increase in the risk of depression for women (Macías-Cortés et al., 2015). The perimenopausal period is marked by intense fluctuation of hormones specifically characterized by the rise in concentration of the pituitary gonadotropin follicle-stimulating hormone (FSH), which is related to the drastic decline of gonadotropin-sensitive ovarian follicles prior to menopause taking place (Macías-Cortés et al., 2015). Studies have shown that there is a strong correlation between menopausal transition and depressive symptoms. Individualized homeopathic treatment (IHT) has been used as a successful form of treatment for MDD related to transitions in menopausal states for women, especially in regards to compliance due to the lack of severe side effects and low cost. IHT for MDD has been proven through observational studies to be associated with improvement of symptoms of menopause that are associated with MDD (Macías-Cortés et al., 2015). Macías-Cortés et al. (2015) performed a study to examine the
efficacy and safety of homeopathic and fluoxetine treatment for MDD associated with peri- and postmenopausal woman in comparison to each other with relations to placebos. The study was performed as a randomized, placebo-controlled, double blind, double dummy, superiority, and three-arm trial with a 6-week follow-up study, with the conditions classified into three groups: IHT plus fluoxetine dummy (homeopathic group), fluoxetine treatment plus IHT dummy (fluoxetine group), and fluoxetine placebo and IHT placebo (placebo group). The efficacy of each condition was based on individual’s change in mean total scores on the HAMD-17, Beck Depression Inventory and Greene Scale, also with regards to safety and remission rates after 6-weeks. The results showed that the IHT group was more effective than the placebo, which was shown through a 5-point difference on the HAMD-17. There was a significant difference in response rates between the groups, where the fluoxetine group showed a greater response rate than the placebo group, but a weaker response rate than the IHT group. Remission rates were relatively similar for the IHT and fluoxetine groups, while both were significantly different than the placebo group. The IHT group was shown as superior to the placebo group through an 8.6 difference on the Green Climacteric Scale, but the fluoxetine group did not show a significant difference to the placebo group. This study shows that homeopathy and fluoxetine treatment for MDD, in regards to menopausal transitions, are both effective in relieving depressive symptoms. One of the key findings of this study is the difference in efficacy between homeopathic treatment and placebo treatment, suggesting that homeopathic treatment is more than just a placebo effect and is potentially more effective than fluoxetine. While this key finding is important, it must be noted that it is based on the Greene Climacteric Scale, which is used to measure core climacteric symptoms specifically for menopausal states; therefore, this finding may only be associated with menopausal transitions.
Individuals have sought the use of CAMs because of the anti-depressant-like effects that occur without unwanted adverse side effects of anti-depressants. The studies presented on homeopathy suggest that the efficacy of the treatment is not simply due to the placebo effect. With this being said, the lack of significant amounts of clinical trials does not help validate these findings. Homeopathy is an individualized form of treatment, which makes it harder to produce concrete, robust evidence. The studies presented on TCM, in regards to acupuncture, suggests that acupuncture is an effective form of treatment for MDD, where as in some conditions it can be considered more effective than orthodox methods of treatment.

The studies presented suggest an important aspect to CAMs that may relate to its efficacy, and that is the overall higher compliance by patients with the use of CAMs in comparison to orthodox methods of treatment. The success of any treatment is limited by the compliance of the patient and their overall belief that the benefits of the treatment they are given out way the costs treatment. Another reason that might relate to the high efficacy rates of CAMs and overall high numbers of individuals seeking CAMs is that homeopaths do not clinically diagnose individuals with MDD; therefore, there is not a negative social stigma or consequence taken on by the individual that is associated with being diagnosed or labeled with MDD.

Overall, the studies presented show that homeopathy and TCM are effective means to treat depressive symptoms, but they lack significant amounts of clinical research to further strengthen the presented findings.

Discussion

The purpose of this literature review is to examine the most effective method to treat the symptoms of MDD, in regards to regulating and improving the neural mechanisms and behavioral / cognitive impairments associated with patients diagnosed with MDD.
Pharmacological treatment works on fixing the biological factors attributed to low levels of 5-HT. SSRI antidepressants have shown to be the most effective pharmacological treatment for MDD because it has the most selective effects on 5-HT, which allows for the minimization of adverse side effects. Pharmacological treatment faces problems with treatment concordance for patients potentially due to the adverse side effects of antidepressants and the cost of antidepressants. These problems with concordance to pharmacological treatment could attribute to the high relapse rate after four months of pharmacological treatment. The use of biomarkers to predetermine an individual’s responsiveness to specific antidepressants can be essential to increasing the efficacy of pharmacological treatment because patients with MDD would be prescribed the most effective antidepressant for that patient; thus, potentially leading to an individualization of prescribed drugs and their effects on patients. Pharmacological treatments are more effective than other methods of treatment because of the ease of treatment, in regards to only having to take a pill for treatment instead of constantly having to meet with therapists or go through complex methods of treatment. It is very time-efficient way to treat MDD because the individual does not have to build relationships with therapists or take time to learn methods of coping.

Combination therapy of antidepressants has shown to be a more effective pharmacological approach to treating the symptoms of MDD in comparison to monotherapy with a single antidepressant. Combination therapy also helps to offset adverse effects because it allows for the use of lower levels of antidepressants, which lessens the potential for using toxic concentrations of antidepressants. Lower levels of antidepressants allow for the individual to stay responsive to the antidepressants, where as high levels of antidepressants can lead to a lack of response to the antidepressant due to overstimulation of 5-HT. Combination therapy can also be used to combine...
novel drugs to produce antidepressant-like effects that do not have adverse effects that have been attributed to the conventional antidepressants.

Behavior treatment has been shown as an effective means to treat the symptoms of MDD by focusing on the cognitive impairments that are associated with MDD. Behavior treatment, even though being focused on the cognitive impairments, has shown effective treatment of symptoms of MDD, which have been associated with neurobiological changes. Behavior treatment has shown to have similar treatment effects as pharmacological treatment, but studies show that there are differences in neurobiological changes, while still providing treatment for the same symptoms. Behavior treatment presents the notion that top-down processes can regulate cognitive impairments for patients with MDD, in regards to behavior treatment acting on a different 5-HT pathway than pharmacological treatment. Treating dysfunctional attitudes is a key goal for CBT and has been proven to be a mediator for MDD for CBT treatment, in regards to the cognitive mediation model, which states that changing cognitive dysfunction will cause a decrease in symptoms of MDD. Studies of cognitive impairments show that learned helplessness and conditioned defeat, or social defeat in humans, effect more than just cognition, but also have a neurobiological basis that causes changes in the 5-HT pathway. Also, the combination of multiple behavioral techniques helps to improve the overall efficacy of treatment, which is similar to that of combination within pharmacological treatment. Behavioral treatment is effective in decreasing relapse rates and increasing remission rates because it provides the individual with the ability to self-treat during depressive episodes that occur spontaneously in one’s life. Behavioral treatments ability to teach individuals coping methods / strategies and treat cognitive impairments gives individuals confidence in themselves by giving the ability to control
their symptoms of MDD by executing coping methods / strategies when depressive episodes occur.

The use of CAMs as a method of treatment for MDD have proven, through the studies presented, to be effective in alleviating the symptoms that are associated with MDD. Homeopathic and TCM have shown to be as effective and in some cases more successful in treating the symptoms of MDD. Individuals exhibiting symptoms of MDD have actively sought out CAMs as a method of treatment because the safety, cost-effectiveness, and overall effectiveness of the treatment. The use of CAMs as effective means to treat MDD have not had enough clinical trials performed to adequately prescribe as a valid treatment for MDD. Successful results of homeopathic treatment are often based on self-report, or are paired with the use of other forms of treatment. Homeopathic treatments act as placebo because some of the methods used are based on “natural” effects of the body to heal itself. The effects of homeopathic treatment on symptoms of MDD have been attributed to that of the placebo effect, but studies have shown that CAMs are more effective than placebos; thus, suggesting that the efficacy of CAMs to treat the symptoms of MDD are attributed to more than a placebo effect. CAMs are attractive to individuals that exhibit symptoms of MDD because homeopaths or acupuncturists do not diagnose the individuals with MDD, which means that there are no adverse social stigmas that come from seeking treatment for symptoms like tiredness, insomnia, or others associated with MDD. Being diagnosed with MDD can have social impacts on the individuals life that might make the individuals wary of self-reporting having symptoms of MDD. CAMs allow for a safe environment for the individual to seek potential treat for symptoms associated with MDD without being labeled as mentally ill due to being diagnosed with MDD.
Pharmacological, behavioral, and CAM treatments have all shown to be effective in treating the mechanisms and behavioral / cognitive impairments associated with patients diagnosed with MDD. These methods all work in different ways that help to regulate low concentration levels of 5-HT that are associated with MDD. Pharmacological and behavioral treatments for MDD are the only ones that have been clinically proven to effectively treat the symptoms associated with MDD, and are the only methods that can confidently be prescribed to individuals with MDD. With that being said, CAMs are effective in treating MDD, but should only be prescribed if orthodox methods of treatment are found to be inadequate, ineffective, or issues with compliance to the treatment arise. Pharmacological and behavioral treatments are two methods that can be used in concurrence with each other that could lead to synergic effects that will increase efficacy of the treatment. Using behavioral treatment in congruence with pharmacological treatment can allow for the use of lower doses of antidepressants, which will help to lower the chance of adverse effects associated with higher levels of antidepressants, or overdependence of on the drug. The use of these two methods together can be used to lower an individual’s dependence on antidepressants, especially if patients are at risk to exhibit symptoms of drug abuse. As mentioned earlier, lower levels of antidepressants can allow for prolonged response rates to antidepressants because overstimulation or toleration to the antidepressant does not occur for the low levels of antidepressants. The process for the individual to learn coping methods / strategies or ways to naturally regulate levels of 5-HT takes time, but the use of low doses of antidepressants can help to speed this process up, in regards to taking the drugs in concurrence with CBT to allow for the neural association of the increase of 5-HT to be associated to the CBT.

MDD is a mood disorder that has multiple factors that are associated with its onset, but most causes stem from low 5-HT concentration levels. Pharmacological and behavior therapy are both
Effective methods in treating the symptoms of MDD by acting on the 5-HT pathway, but each method produces its effects on different 5-HT pathways. CAMs requires more research before it can be clinically prescribed and tested, but studies show that it is an effective means to safely treat MDD, while providing a socially safe environment for the individuals to be treated. Overall, the combination of pharmacological and behavior treatment potentially allows the 5-HT pathway to be facilitated in different areas, which could cause synergic effects on efficacy of treatment.
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