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Gillian Chambers  
*Liberty University*

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**To Heal a Mind: A Functional Approach to the Treatment of Major Depressive Disorder**

Gillian Chambers

School of Nursing, Liberty University

NURS 306: Pharmacology II

Dr. Deidra Simpson

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## **Introduction**

With 21 million Americans afflicted with major depressive disorder (MDD) every year, the Western healthcare system is fighting to gain ground against this mental health crisis. Medical professionals worldwide have largely turned to pharmaceutical treatments of this disorder: from 2005-2018, antidepressant use climbed from 11% of the population to 13.2% (CDC, 2011; CDC, 2020). However, the medications most commonly prescribed for MDD have been found to be not only less effective, but also more dangerous, than previously believed. Research even reflects that some of these medications could be potentiating depression and worsening its effects. Fortunately, much investigation has been done into alternative methods of MDD detection, prevention and treatment through other methods. Many of these methods are seen as more holistic or naturopathic, while some are reliant on behavior modification from the patient, potentially resulting in less utilization of these methods. With good research reflecting the efficacy of these methods, it is important to perceive them as serious and beneficial treatments for the MDD sufferer, and to select the one that will best fit the patient for their needs.

## **Assessment and Root Cause**

Ideally, before ever diagnosing a patient with MDD, a blood workup and full detailed assessment should be conducted. MDD cannot be diagnosed off a blood test or other laboratory test, but instead utilizes screening tools such as the Patient Health Questionnaire-9, or the PHQ-9 (Bains & Abdijadid, 2023). The PHQ-9 reflects 9 of the DSM-5 criteria for the diagnosis of MDD, and is particularly useful as a self-reporting tool. Behavioral aspects of depression are also often used to clarify the diagnosis, especially between subtypes of depression. Characteristics of MDD include sleep changes, anorexia or binge eating, feelings of fatigue or malaise, lack of interest in activities, emotional lethargy and thoughts of despair or death (Williams &

Nieuwsma, 2023). Finally, MDD needs an in-depth history: ideally medical, familial, social and behavioral histories are all included. The focus is generally to determine if depression is a recurring pattern, and if mania or hypomania are involved. At least one period of depression lasting two weeks is required for MDD to be diagnosed.

There are many existing conditions which are known to cause emotional fluctuation and depressive thoughts or actions, which can be discovered through physical examination (Discovery Mood, 2024). Hypothyroidism suppresses the thyroid, causing metabolism to slow, which causes extreme fatigue, weight gain, anorexia and emotional lability. Hypercalcemia, a disorder resulting from a hyperactive parathyroid, elevates levels of calcium in the blood to dangerous levels (Nagy et al., 2020). As many neuropathic processes are regulated by calcium, hypercalcemia can mimic depression with cognitive changes, memory loss and decreased affect. Similarly, vitamin D deficiency will cause hypocalcemia, affecting neurological functions and causing severe exhaustion (Discovery Mood, 2024). This also can closely mimic depression, causing sleep changes and cognitive loss of function. Diabetes mellitus can also cause depression-like symptoms, particularly if it takes the form of type 2. This is because glucose absorption into the cells to be used for fuel is impaired, causing the deprivation of neural cells from fuel sources. This slows the function of the brain, causing neurological symptoms such as delayed cognitive function, fatigue and frustration. Finally, adrenal fluctuation or other hormone imbalances can cause severe emotional distress and physical malaise, leading to a potential MDD diagnosis when the true issue originated in the endocrine system (Harding, 2023).

These are some key examples of disorders that can cause depression-like symptoms without being neurological in origin. An excellent pre-diagnosis solution is to carry out an extensive assessment. This ought to be done via physical assessment, but additional labs are

crucial to discovering unknown root disorders: blood work can catch elevated or reduced T3/T4 for thyroid problems, while a urinalysis can detect potential diabetes. A CT scan or MRI can be taken if the patient is also complaining of headaches, personality changes, or other neurological symptoms. Another useful lab to take would be the dexamethasone suppression test, which is positive in Cushing's disease (a condition with severe emotional effect) but also positive in depression (Halverson, 2024). Finally, toxicology labs should be drawn to ensure that the patient is not struggling with substance abuse, which can cause severe emotional lability and depression.

### **Lifestyle Change as Treatment for MDD**

Lifestyle changes are well known to be one of the most major, significant treatments to improve life in general, not just for MDD. A 2007 study asked patients to self-report the interventions they found to be the most effective in the treatment of their depression symptoms (Parker & Crawford, 2007). 31 strategies in total were surveyed on. Patients consistently rated self-help and coping strategies more highly than antidepressants or seeking professional help, with exercise ranked "extremely highly" in the list. Counseling and relaxation strategies also sat near the top of the list, while antidepressants and psychotherapeutic strategies were listed as "moderately helpful". Interestingly, this significantly contrasted with how professionals tended to rank interventions. Distraction strategies were considered best by providers, with pharmaceutical medication ranked third, and exercise coming in near the bottom of the list. The study recommended that for MDD specifically, the therapies rated highly by the patients should be investigated further for their low-cost, seemingly high-efficacy impact. In line with these findings, other studies have shown that 6 different forms of lifestyle modification are extremely effective at preventing and mitigating depression symptoms, if not causing remission (Piotrowski et al., 2021). These six forms are (in no particular order of importance):

1. Regular exercise
2. Restorative sleep
3. Whole and healthy diet
4. Management of stress
5. Avoiding substance abuse
6. Positive social networks

With focus on these factors, the patient's lifestyle would be considered 'healthy', and depression incidence would reduce drastically. Avoiding substance abuse is generally avoided in all patients, regardless of mood disorder or not. Positive social networks can be encouraged by the healthcare provider, but it is more difficult for them to influence the social areas of a patient's life than if a licensed therapist was working with the patient. Stress management can be influenced both by the provider and the therapist, but is perhaps more beneficial when the therapist works with the patient to develop strategies. Of the 6 points, 3 of them are more critical for the provider to specifically address: exercise, sleep and diet.

Exercise has been consistently ranked one of the highest natural treatments for depression that exists (Noetel et al., 2024; Kim, 2022; Murri et al., 2018; Schuch et al., 2016). Murri and others write that exercise seems to be the most productive if it is aerobic, in a group, and led by an instructor (2018). They add that this is likely because it is beneficial for both the mind and body. Exercise reduces inflammation, improves ANS control by activating the sympathovagal response, restores cardiorespiratory fitness, and reduces weight, which regulates metabolism and appetite. Mentally, exercise releases endorphins, which in turn release a flood of serotonin, norepinephrine and dopamine, often allowing the depressed individual to feel awake and invigorated (Kim, 2022). Exercise can also shift an individual's focus from feeling out of control and despairing, to giving them a sense of accomplishment and well-being after completing something taxing (Mayo Clinic, 2023). Additionally, establishing a habit of exercise will also induce self-esteem and confidence in the depressed individual, because they can acknowledge that they have had to build resilience over time (Kim, 2022). The types of exercise that have

been proven to be the most effective for depression mitigation are aerobic training (i.e., cycling or walking) and strength training (i.e., lifting weights) (Moraes et al., 2020; Bergin & Amaladoss, 2020). A pattern of exercise 2-3 times a week for 30 minutes each time was concluded to be generally most effective, especially when conducted at moderate intensity. Others agree in the principle and in the exercise intensity, but increase the number of times exercise should be conducted to 30 minutes every day (Ranjbar et al., 2015).

How, though, should a provider prescribe exercise? The most obvious concern is adherence to a program, as it is the sustained benefits over time that are impactful for long-term depression prevention (Bergin & Amaladoss, 2020). Good strategy would consist of keeping to the types of exercise that will be most effective for combatting depression, but also working with the patient to determine what their preferences are. Barriers to exercise must also be considered, particularly if the patient has other health challenges. Breaking down exercise into manageable portions for the patient would be especially useful: for example, instead of telling them that they must achieve at minimum 150 minutes of aerobic exercise per week, ask them to walk for 30 minutes on their lunch breaks during the work week. Another study adds that a good way to retain interest and investment into the exercise is to have it be a group exercise program, led by an instructor, or to involve dance or competition (Ranjbar et al., 2015).

Additionally, work with each patient to determine their motivating factors (Bergin & Amaladoss, 2020). Stress how much exercise can elevate mood, and encourage working out with others as a socially beneficial event, which has been proven to increase self-reporting of good health. Also, if the patient is currently struggling with their health, a good tactic would be to encourage them to increase their exercise over time. The patient can start by going for a walk 1-2 times a week, and increase that to 5 or 6 days over time, or they could eventually work up to

jogging instead of running. Some patients are more motivated to train in strength: encourage them to receive training, and focus on whole-body strength building exercises 2-3 times a week for no more than 45 minutes at a time (to avoid injury). If the provider bears in mind these strategy points and has an open conversation with the patient, seeking to develop a plan they will enjoy, it will be significantly more likely that the patient will adhere to the treatment plan.

On a similar topic, insomnia is a major risk factor for developing depression, and a common symptom of those suffering from MDD as well. Sleep is well proven to have a distinct effect on mood and sense of well-being, with impaired sleep leading to negative coping and increased sensitivity (Riemann et al., 2020; Triantafyllou et al., 2019). The effect of sleep quality to improve mood significantly outweighs the effect of mood on sleep quality (Triantafyllou et al., 2019). In other words, for a patient who is depressed, getting better sleep will improve their mood more than improving their mood will help their sleep. When MDD patients' sleep was studied, serious sleep disturbance was found, far more than in healthy individuals. Both insomnia and hypersomnia were found, though insomnia was discovered to have worse impact on mental health than hypersomnia. Another study found that impaired sleep in MDD slowed psychomotor function, reducing physical and mental functionality overall (Wilckens et al., 2020).

Fortunately for those struggling with insomnia, there are several options for treatment, with one especially effective type. Cognitive behavioral therapy for insomnia (CBT-I) are teaching sessions, generally ranging from 30-90 minutes long, that educate an insomnia patient on how to fall asleep, stay asleep and achieve better sleep (Walker et al., 2022). These sessions occur usually 6-8 times, generally until the patient has 'bought in' to the therapy type and is hopefully demonstrating better sleep. Efficacy is clearly demonstrated to be effective, causing at least a 50% post-treatment symptom reduction with effects lasting up to 2 years after treatment



has been conducted. Research even shows that it is more useful than sedative medications in the long-term, which is especially useful for patients with comorbid disorders such as MDD. The U.S. and Europe both consider CBT-I to be a first-line treatment, rather than prescribing a medication (Riemann et al., 2020).

These treatments are more effective when research describing the treatment's efficacy to help with MDD is considered. In patients with high MDD risk factors or recurrent MDD episodes, CBT-I treatment found significantly decreased rates of MDD onset (Boland et al., 2023). This has been found especially effective in MDD prevention in older adults: in a study's three-year follow up period after patient CBT-I administration, a 60% reduction in development of depression was calculated (Irwin et al., 2022). CBT-I has been proven to reduce depressive symptoms in older adults who were suffering from concurrent insomnia and MDD, with maintained efficacy upon follow-up appointments (Sadler et al., 2018). Most interestingly, a 2008 randomized control study found that SSRI administration to patients with insomnia and MDD was twice as effective when CBT-I treatment was being administered simultaneously (Manber et al.). However, despite these exciting findings, more research is needed on this topic to determine definitively if CBT-I should be treated as a component of a depression protocol.

One crucial but often overlooked aspect of depression is the patient's diet. Of course, eating healthy is well recommended to every patient: reducing junk food, increasing plants and proteins, and focusing on 'whole' foods that are less processed than the others are all highly recommended interventions (Opie et al., 2015; Selvaraj et al., 2022). Processed foods high in fat and sugar, can cause obesity and inflammation, which – as discussed in the exercise section – all contribute to impaired cognitive function. High amounts of red and processed meats were indicated to cause higher incidence of depression. Whole foods such as organic fruits, vegetables

and grains have fewer chemicals in them, and the body processes them more easily, reducing inflammation. Increasing plants and proteins provides necessary building blocks for the body to heal and supply the brain with its proper glucose and other needed nutrients. If the patient does not understand good nutrition versus poor diet, they will cause harm to their mental wellbeing, so patient education is important. One study found that even a 3-week diet intervention in young adults, reducing inflammatory foods and emphasizing whole foods and vegetables, was enough to significantly reduce depressive symptoms (Francis et al., 2019). This reduction in symptoms remained persistent at a 3-month checkup. Along with the diet change, the researchers educated participants on proper diet and cravings control, which may have helped with long-term results.

For diet treatment more focused on MDD, the Mediterranean diet was also found by most studies to be particularly advantageous to prevent or mitigate depression (Opie et al., 2015; Jacka et al., 2017; Selvaraj et al., 2022). Selvaraj and others even state that their findings indicated high adherence to the Mediterranean diet causes depression incidence to decrease by 30%. This seems to be because the Mediterranean reduces systemic inflammation, as can be seen in reduced CRP and IL-6 markers from the diet's population (Zielinska et al., 2022). The Mediterranean style of eating contains high amounts of polyphenols, antioxidant compounds that work to counteract damage to the body from many different antagonists. Among their many beneficial functions, polyphenols seem to help regulate the microflora of the gastrointestinal tract, which has significant ramifications upon mental status, as well as combating general inflammation. Polyphenols can be found in many plants and fruits, such as blueberries, cocoa and olives. Fatty acids such as omega-3s are also present in high quantities in the Mediterranean diet, due to the large fish and nut intake. The most beneficial omega-3 fatty acids for the brain are eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA), which have already been

established as a possible treatment for mood disorders such as MDD, though research on this subject tends to conflict on how beneficial these substances are on their own (Mischoulon, 2020). These fatty acids are anti-inflammatory, and they seem to reduce levels of cholesterol and inflammatory markers in the body, decreasing systemic stress and boosting psychomotor function (Wani et al., 2015). Additionally, the Mediterranean diet focuses more on whole foods and vegetables, adhering it closely to the ideal diet.

Aside from a beneficial basic diet, there are many substances that are important to consider giving as a supplement. This is why thorough and complete blood work should be drawn – if the provider has adequate understanding of dietary deficiencies and low levels of nutrients or vitamins, then they will be able to prescribe or recommend substances that are needed in each patient. There is no better illustration of this principle than calcium deficiency or surplus, as discussed above. This abnormality is easily corrected: in patients with hypocalcemia, depressive symptoms are negatively associated with increased calcium intake, forcing MDD remission when adequate calcium is taken in by the patient (Shen et al., 2023). Another notable electrolyte that can cause depression in a deficit is magnesium (Moabedi et al., 2023). Magnesium is critical for synthesis and action of many, many enzymes in the body. It also naturally antagonizes the NMDA receptors in the nervous system, which helps regulate the balance of GABA and glutamate in the body, allowing for better emotional balance (Lee, 2023).

Of all supplements consistently appearing in research for mitigation of MDD, two recur frequently: probiotics and PUFAs (omega fatty acids). Evidence is clear that the microbiome of the GI tract has an impact on mood and neurological functioning, and probiotic use has been proven to have a regulatory effect on both microbiome and mood (Kelly et al., 2016; Huang et al., 2016). *Lactobacillus* and other common probiotic strains are useful, but research cautions

that individual groups of probiotics should be tailored to each patient's profile for best microbiome regulation (Gao et al., 2023). Foods naturally high in probiotics, such as yogurt and kefir, would be excellent for incorporation into the patient's diet as well. PUFAs are a combination of the omega-3s covered earlier, EPA and DHA, generally in a 2:1 or 3:1 formulation (Thurfah et al., 2022; Liao et al., 2019). These fatty acids reduce inflammation, suppress eicosanoids, and combine into phospholipids for cellular reproduction. EPA also supports neuroprotection and partially increases neurotransmission of serotonin and dopamine. Though PUFA administration is not conclusively demonstrated to be effective in monotherapy for MDD, it is certainly useful in augmentation of other therapies and as a supplement in general.

### **Conclusion**

Though MDD is still growing in frequency and severity in the Western world, therapies are becoming more available and low-cost rapidly. Many lifestyle changes can be exerted to reduce MDD, with three types of particularly effective habits. Exercise is not only beneficial for the body, but also the mind, as one of the single most effective treatments for depression known. Sleep is critical to the regulation of the mind, and while being extremely beneficial to the MDD sufferer to treat, the patient will also desire more of it, making it a highly motivated symptom to target. Diet is more crucial than often considered, and both dietary framework and supplements are proven to have significant effect. There are many, many more that are beneficial and life-changing which deserve a far deeper and closer examination than could be provided here. However, there should be enough research to suggest that perhaps lifestyle change should be considered in step with, or even before, serious pharmaceutical treatment of MDD. Low to no cost, long-term benefit, and eventual prevention of further MDD episodes should be compelling for the provider to consider as one of the frontline therapies for this debilitating disorder.

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