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Biological Mechanisms of Major Depressive Disorder: Exploring Neural Circuits and Neurotransmitter Systems in Diagnosis and Treatment

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ABSTRACT

Major Depressive Disorder (MDD) is a severe mental illness characterized by persistent low mood, impaired cognitive function, and disrupted emotional regulation. The development and maintenance of MDD involve complex interactions between neural circuits and neurotransmitter systems. This paper provides a comprehensive review of the biological underpinnings of MDD, focusing on how dysfunctions in neurotransmitter systems and neural circuits contribute to the disorder. Key neurotransmitters, such as serotonin, norepinephrine, dopamine, glutamate, and GABA, and their associated neural circuits, including the amygdala, prefrontal cortex, hippocampus, and hypothalamic-pituitary-adrenal axis, are examined for their roles in the pathophysiology of MDD. The research also explores recent advances in treatment approaches targeting these systems, including pharmacological interventions like SSRIs, SNRIs, and ketamine, as well as neuromodulation techniques such as Transcranial Magnetic Stimulation (TMS) and Electroconvulsive Therapy (ECT). Through an extensive literature review, this study highlights the importance of understanding the biological mechanisms underlying MDD to develop more effective therapeutic strategies. By identifying and addressing these mechanisms, the research aims to improve treatment outcomes and enhance the quality of life for individuals suffering from this debilitating condition.

Introduction

The development and maintenance of MDD involve complex interactions between neural circuits and neurotransmitter systems. Neural circuits are populations of neurons connected by synapses to carry out a specific function, and neurotransmitters are signaling molecules, sometimes ligands, secreted by neurons to affect cells across synapses. A shift or dysfunction in one of these systems can lead to effects that contribute to the initiation and persistence of depression.

Understanding the biological causes of MDD is a key factor in developing effective treatments to help those diagnosed with this illness. This knowledge helps to create better therapeutic approaches and medical interventions, ultimately aiming to improve the quality of life for individuals suffering from MDD.

In a study conducted by Dr. Sawchuk (2022), he explored the significance of neural circuits and neurotransmitters in depression. Through their research, they found that differences in neurotransmitter function and their interactions with neural circuits play a role in depression. Specifically, they found that inflammatory cytokines–signaling molecules produced by the immune system in response to injury or infection– can affect serotonin, dopamine, and glutamate neurotransmitter systems. By disrupting the function of these systems, they contribute to the neurodegenerative changes observed in depression. For example, the reduction in the integrity of the prefrontal cortex is affected by inflammatory cytokines. This part of the brain is important for functions such as decision-making and the regulation of emotions.

Another remarkable study done by Yale Medicine discusses the role that norepinephrine, glutamate, and GABA(neurotransmitters) play in mood regulation. Stress and anxiety can disrupt the connections between nerve

cells, and synapses, leading to disruptive communication and a loss of neural connection. This overall process is believed to contribute to the development of depression. This research can help experts further understand the biology behind depression and develop a long-term treatment for it (Krystal & Katz, 2021).

A regional study conducted in New Jersey did a similar study but they focused on the role of brain-derived neurotrophic factor(BDNF), a protein that plays a crucial role in the growth, maintenance, and survival of neurons in the brain. It is involved with neuroplasticity, which lets the brain adapt and learn. It is specifically important to the hippocampus and is essential for long-term memory. Playing an important role in mood regulation, reduced levels of this protein have been linked to various neurodegenerative disorders including depression. Studies have proved that stress and depression can lower BDNF levels, while treatments such as antidepressants and exercise can increase BDNF expression.

Each of these studies has researched a biological component behind depression. They have found the role that a specific neurotransmitter, circuit, or protein plays in the instigation or development of depression. The primary goal of my research is to define the biological processes behind depression: specifically the contribution of neural circuits and neurotransmitters. Identifying these processes can help find effective cures and treatments for depression that can change the lives of patients suffering with this mental illness.

Methodology

The purpose of this paper is to provide an overview on what Major Depressive Disorder (MDD) includes biological causes, risk factors, and diagnosis and testing. This paper has a focus on the neurotransmitter systems and neural circuits that play a role in the development of MDD and treatments that specifically target them. The method used to write this paper is a review of literature. Multiple sources such as PubMed and Google Scholar were used. Introduction- Depression is not a social media trend nor a make-believe illness society claims to exist. Depression, also known as major depressive disorder (MDD), is a serious medical illness that affects a person's thoughts, behavior, feelings, and sense of well-being (National Institute of Mental Health, n.d.). Symptoms include isolation from friends and family, increased anger or irritability, feeling restless, being withdrawn, and increased use of drugs.

Review of Related Literature

Major Depressive Disorder (MDD)

Major Depressive Disorder is a common and serious mental illness that negatively affects how one feels, thinks, acts, and perceives the world (Onyemaechi, 2024). This condition impacts various aspects of a person's life, overwhelming everyday tasks. The illness is often associated with symptoms such as persistent low mood, changes in appetite and weight, sleep disturbances, fatigue, feelings of worthlessness or excessive guilt, and recurring thoughts of suicide or death (Nemeroff & Schatzberg, 2014).

Persistent low mood makes it difficult for individuals to find joy or interest in activities they once enjoyed. Changes in appetite and weight can involve significant increases or decreases, leading to noticeable weight fluctuations. Sleep disturbances include insomnia, where individuals find it hard to fall or stay asleep, and hypersomnia, where they sleep excessively but still feel fatigued. Fatigue and a lack of energy make daily activities challenging. Emotional symptoms include feelings of worthlessness or excessive guilt, leading to self-criticism for perceived failures.

One of the most concerning symptoms of Major Depressive Disorder is recurring thoughts of suicide or death. These thoughts can range from passive wishes of not wanting to wake up to active planning or attempts at taking one's own life. MDD is a clinical diagnosis, and doctors attempt to diagnose it with a medical history, family history, substance use history, and a mental health examination. Patients brought by concerned family members or

social workers often deny having any symptoms.

Biological Causes of MDD

Major Depressive Disorder not only has environmental causes but also biological causes. Patients who are diagnosed with MDD often have abnormal brain scan activity. Research conducted by the National Institute of Health shows that a person diagnosed with depression may lose gray matter volume in the brain. For example, previous studies have proved that the thickness of the right medical orbital cortex in MDD patients is thinner than that in healthy controls. During treatment, decreased cortical thickness was found in the OFC in MDD patients.

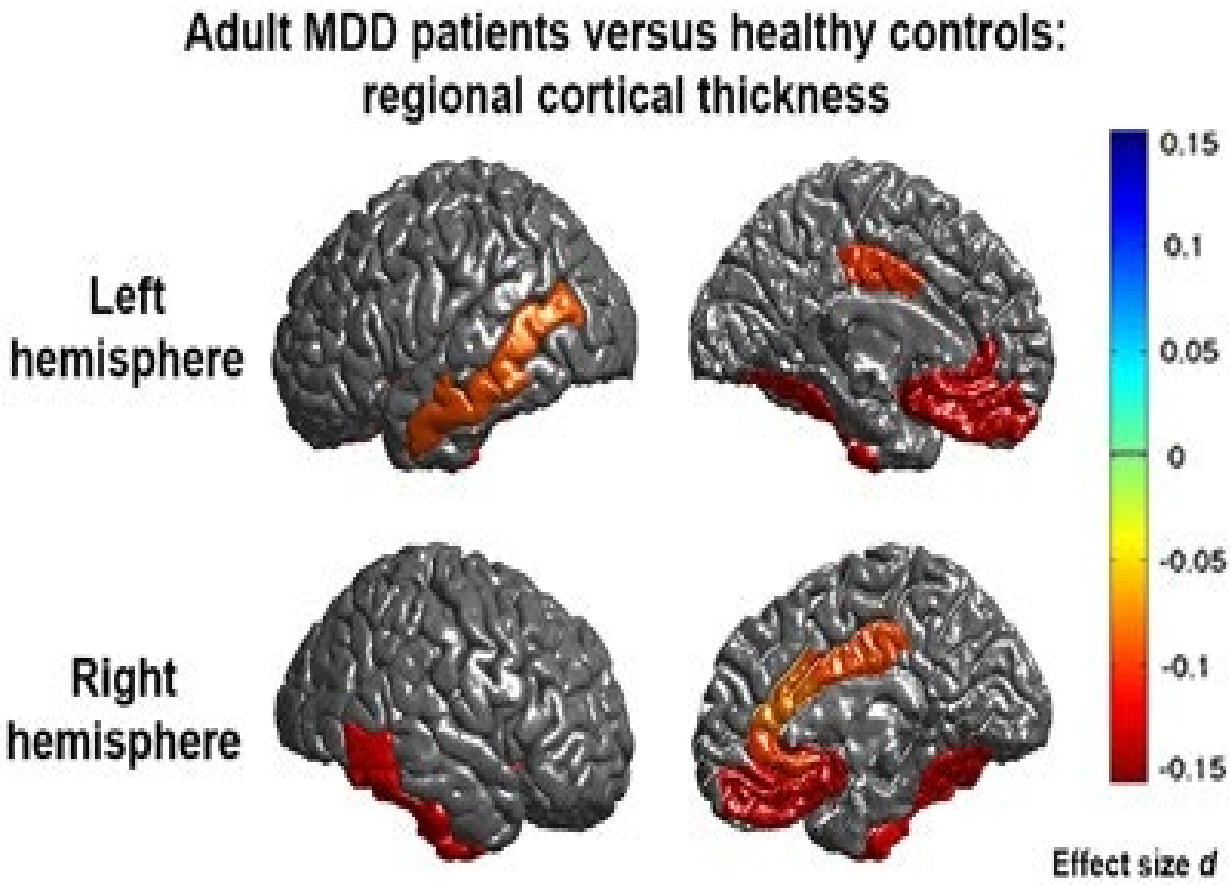

Figure 1. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group
Source: Nature.com

Neuroimaging research shows that human intellectual ability is related to brain structure including the thickness of the cerebral cortex. Most studies show that general intelligence is associated with cortical thickness in areas of the association cortex, a part of the brain that is responsible for complex cognitive functions (Cotman & McGaugh, 1980), distributed throughout both brain hemispheres (Menary et al. 2013). An increase in cortical thickness leads to a loss of interest and can affect a person's memory, attention, and ability to think, all signs of depression (Cartreine, 2016). Depression also causes the hippocampus to raise its cortisol levels which impedes the development of neurons in the brain (Amiel, n.d.). These findings underscore the complex interplay between environmental and biological factors in MDD, highlighting the importance of comprehensive approaches to understanding and treating this disorder.

Risk Factors

While a person may be diagnosed with MDD without any risk or genetic history of it, there are specific risks that increase the possibility of a person getting diagnosed. Having a family history of depression can increase the risk of developing MDD. People with a parent or sibling with major depression have a two to three times greater chance of developing MDD than the general population (Levinson et al. n.d.). This heightened risk suggests a significant genetic or hereditary component in the susceptibility to this disorder. Research has shown that genetic factors can influence the likelihood of developing MDD by affecting how an individual responds to stress and processes emotional experiences, which can make those with a familial history more vulnerable to developing the condition.

Major negative life changes, trauma, or stress can also heighten the risk of MDD. Significant life events such as the death of a loved one, divorce, job loss, or serious financial problems can act as triggers for the onset of depressive episodes. Similarly, experiencing trauma, whether from a single severe incident or prolonged exposure to distressing situations, can have a profound impact on mental health, increasing the likelihood of developing MDD. Chronic stress, resulting from ongoing life difficulties or persistent environmental pressures, can also lead to changes in brain chemistry and emotional regulation, further elevating the risk of major depression.

Adults who are older with depression also have more severe symptoms of other serious illnesses, such as diabetes, cancer, chronic pain, and Parkinson's disease. Aging often brings about a range of physical health challenges, and the presence of these serious illnesses can complicate the experience of depression. The interaction between depression and these other health conditions can exacerbate the severity of symptoms, making the overall health situation more complex. For example, chronic pain or illness can contribute to feelings of hopelessness and helplessness, which can intensify depressive symptoms. Additionally, the physical limitations and discomfort associated with these conditions can affect a person's overall quality of life, further impacting their mental well-being.

In summary, while MDD can occur in individuals without any identifiable risk factors, the presence of a family history of depression, major life changes, trauma, and chronic health conditions can significantly increase the risk of developing this disorder. Understanding these risk factors is crucial for recognizing potential vulnerabilities and implementing preventative measures or interventions to address and manage MDD effectively.

Diagnosis and Test

MDD is usually sought to be diagnosed through questionnaires at annual checkups at the doctor's office. It is considered a clinical diagnosis and is mainly diagnosed by the clinical history given by the patient and mental status examination (Bains, 2023). The clinical interview includes medical history, family history, social history, and substance use history. After this, professionals also rule out any underlying medical or organic causes of MDD (Abdijadid, 2023).

In addition to the initial assessment, standardized diagnostic tools such as the Hamilton Depression Rating Scale (HAM-D) or the Patient Health Questionnaire-9 (PHQ-9) are frequently utilized to quantify the severity of depressive symptoms. These tools help in systematically evaluating the patient's condition and providing a more objective measure of their symptomatology (Cohen, 2020).

Furthermore, clinicians may perform a thorough physical examination and laboratory tests to exclude other medical conditions that could mimic or contribute to depressive symptoms, such as thyroid disorders or vitamin deficiencies (Gordon, 2021). The diagnostic process is often comprehensive and multi-faceted, requiring careful consideration of various factors to ensure an accurate diagnosis.

The assessment process also involves evaluating the impact of MDD on the patient's daily functioning, including their work, relationships, and overall quality of life. This holistic approach helps in understanding the full scope of the disorder and in developing a tailored treatment plan (Miller, 2022). By combining clinical interviews, standardized assessments, and medical evaluations, healthcare professionals aim to provide a thorough and accurate diagnosis of Major Depressive Disorder.

Neural Circuits and Neurotransmitter Systems

Neurotransmitter systems are collections of neurons that use a specific neurotransmitter to send signals through the nervous system.(Kandel et al.) They are crucial for processes in the body such as regulating mood, cognition, and motor function. First, an electrical signal travels down the axon of a neuron, and releases neurotransmitter molecules that bind to receptor sites on another neuron. This signal is picked up by the second neuron and is either stopped or passed along.

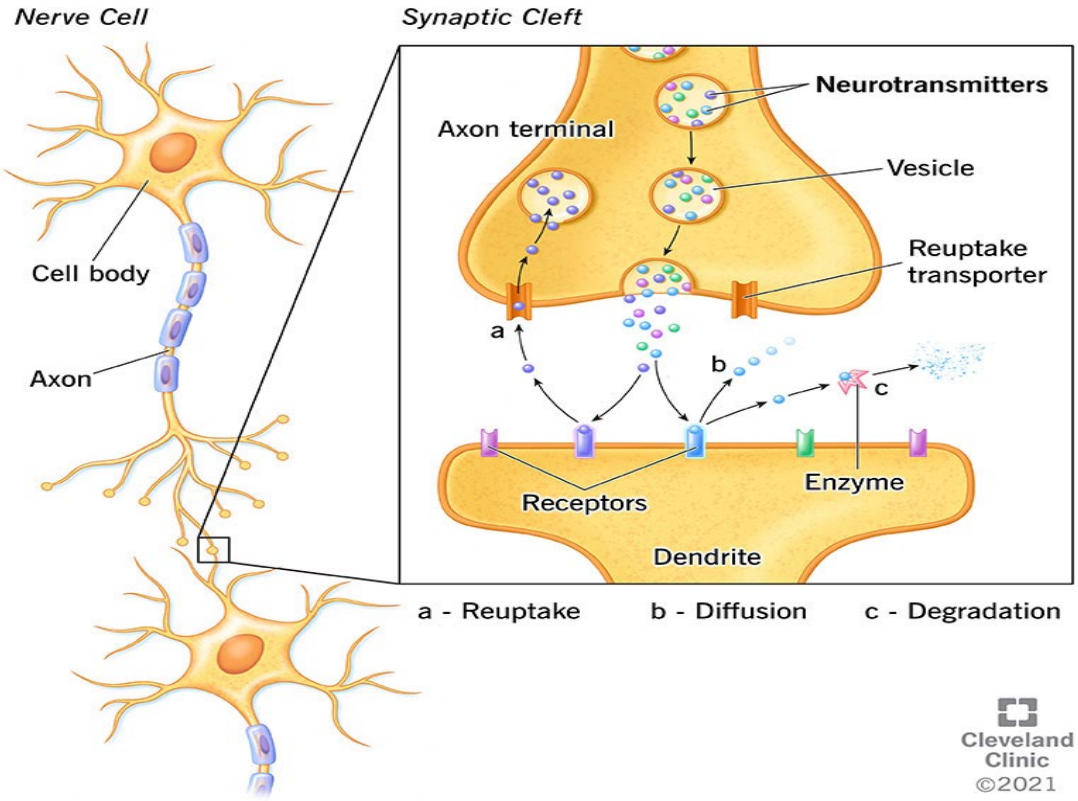

Figure 2. Source: Cleveland Clinic

Since they serve such an important purpose, they also affect the development and regulation of MDD; these include serotonin, norepinephrine, dopamine, glutamate, and Gamma-aminobutyric acid(GABA). Serotonin is essential for the regulation of sleep, learning, memory, body temperature, and happiness(Bakshi, 2020). It's shown that people that are diagnosed with MDD have reduced serotonin transmission causing constant sadness, anxiety, and disturbances in sleep (Harvard Health Publishing, 2019). Low levels of serotonin have also been linked to a higher risk for suicide.

The second neurotransmitter tied with MDD is norepinephrine. It is known to play a role in the body's "fight or flight" response. It regulates mood, attention, and stress response and is essential to maintain alertness and focus. Low levels of this neurotransmitter are linked to poor concentration, a lack of motivation, and fatigue; symptoms of MDD (Cleveland Clinic, 2023).

Next, the most familiar, is dopamine. It is a key neurotransmitter that is involved with the brain's reward system and motivation. A lack of dopamine is associated with symptoms such as anhedonia, the inability to feel pleasure in normally enjoyable activities (Harvard Health Publishing, 2019). Low levels can cause decreased

motivation and overall interest in living. Dysfunction in dopamine can intensify the symptoms of MDD.

Glutamate is an excitatory neurotransmitter and is crucial in cognitive functions such as memory and learning. Disturbed or elevated levels are shown to lead to neuronal damage which causes mood disturbances and an overall increased risk of MDD.

Lastly, Gamma-aminobutyric acid(GABA) is the brain's primary inhibitory neurotransmitter. It promotes relaxation and inhibits excitability. Reduced levels of GABA are often associated with insatiable mood, increased anxiety, and high stress response. Overall it disrupts the brain's ability to regulate emotional responses, leading to constant depressive symptoms.

Neural circuits are networks of interconnected neurons that work together to process information and produce responses. They are involved with motor control, cognitive functions, sensory processing, and emotional regulation. These circuits also play a significant role in depression.

The Amygdala circuit is involved in processing emotions, specifically fear and anxiety. In someone diagnosed with MDD, this circuit can become hyperactive which leads to heightened emotional responses, anxiety, and a focus on negative stimuli.

The prefrontal cortex circuit is responsible for decision making, regulating emotions, and thinking. Reduced activity in this circuit is associated with impaired decision-making, difficulty concentrating, and a worsened regulation of emotions.

The hippocampal circuit is crucial for memory formation. Those who have MDD, might have a smaller/reduced hippocampus than that of a regular brain. This leads to problems with memories and forming new memories. It also contributes to the persistence of negative thoughts.

The hypothalamic-pituitary-Adrenal(HPA) axis contributes to the body's stress response by controlling the release of cortisol, a stress hormone. In someone who has MDD, the HPA axis is usually overactive which can lead to feelings of mood disturbances, chronic stress, and anxiety.

Lastly, the nucleus Accumbens Circuit is part of the brain's reward system and contributes to processing happiness and motivation. Dysfunction in this circuit can lead to anhedonia, as mentioned earlier. Reduced acidity in this circuit can result in a lack of motivation and diminished interest in activities. These circuits are all essential to the function of the brain and when disturbed, can contribute to the development and maintenance of MDD.

Neural Circuits and Neurotransmitter Systems as a Treatment for MDD

Treating Major Depressive Disorder (MDD) has become more focused on the specific brain circuits and chemicals that are out of balance in people with this condition. Medications are still the most common treatment. For example, doctors often prescribe drugs like SSRIs and SNRIs, which help increase the levels of serotonin and norepinephrine—two important brain chemicals—making them more available in the brain. These medications help improve the function of areas like the prefrontal cortex (PFC) and the limbic system, which are often not working properly in people with MDD (Carpenter et al., 2019). Recently, ketamine has been introduced as a new treatment option, especially for those who haven't responded to other treatments. Ketamine works differently by targeting the glutamate system, leading to quick relief of symptoms in some cases (Berman et al., 2000; Zarate et al., 2006).

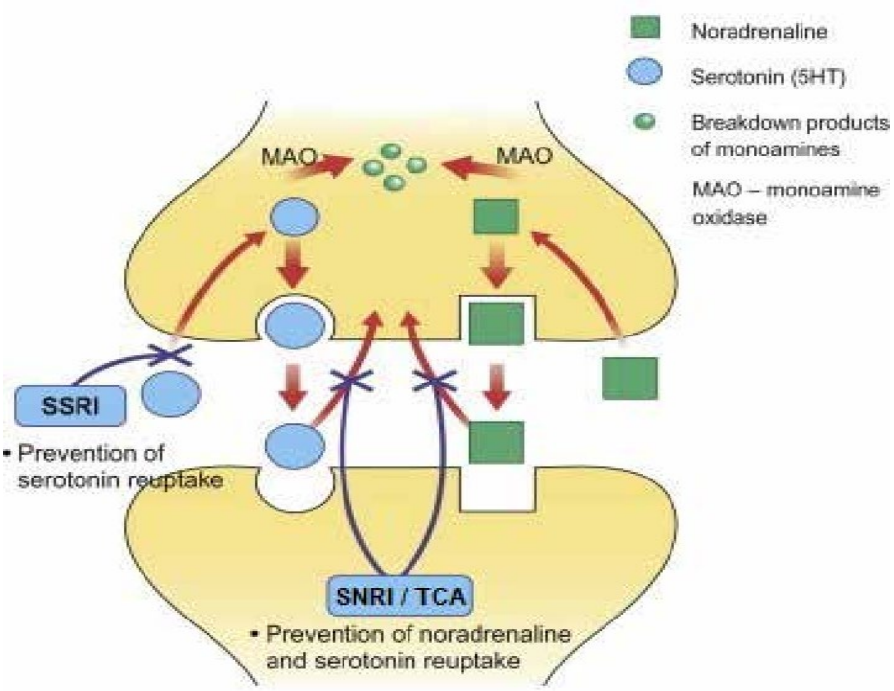

Figure 3. Mechanism of the action of the SNRIs and SSRIs. Source: Research gate

Besides medication, there are also treatments that directly target the brain's circuits. Transcranial Magnetic Stimulation (TMS) is one such treatment that focuses on the dorsolateral prefrontal cortex (DLPFC), a part of the brain that often isn't as active as it should be in people with MDD (O'Reardon et al., 2007). Electroconvulsive Therapy (ECT) is another option, especially for severe cases. ECT works by causing changes in brain areas like the anterior cingulate cortex (ACC) and hippocampus, which can help improve symptoms (Serafini et al., 2015). Another technique being studied is Deep Brain Stimulation (DBS), which targets deeper brain regions that are often involved in depression, although it's still mostly experimental (Mayberg et al., 2005).

Finally, therapy and lifestyle changes are also important parts of treating MDD. Cognitive Behavioral Therapy (CBT) is a common type of therapy that helps people change negative thought patterns, which can also affect the brain circuits involved in mood (DeRubeis et al., 2008). Additionally, regular exercise and mindfulness practices, like meditation, have been shown to improve brain health by boosting neuroplasticity, or the brain's ability to change and adapt, and by balancing brain chemicals (Kandola et al., 2019; Gotink et al., 2016). Combining these different approaches gives a better chance of effectively treating MDD by addressing the various brain-related factors involved.

Ways to Prevent Major Depressive Disorder

Preventing Major Depressive Disorder (MDD) involves a combination of community-based strategies and individual actions that can significantly reduce the risk of developing the condition. Community approaches, such as school-administered programs, play a vital role in this preventive effort. Schools that implement mental health education programs help students build resilience and manage stress effectively. Research indicates that these programs can substantially lower the risk of emotional and behavioral problems (Weist et al., 2007). Similarly, support groups offer essential support by providing a space for individuals to share experiences and receive emotional backing, which can mitigate feelings of isolation and promote better mental health (Cuijpers et al., 2010). Workplace wellness programs also contribute to prevention by integrating mental health resources and stress management initiatives, fostering a

supportive environment that can help prevent the onset of depression (World Health Organization, 2010).

On an individual level, several proactive measures can be taken to reduce the risk of MDD. Engaging in enjoyable activities and hobbies is crucial, as these activities not only provide pleasure but also enhance life satisfaction and emotional resilience (Roshanaei-Moghaddam et al., 2011). Maintaining strong social connections with friends and family is equally important, as these relationships provide valuable emotional support and reduce feelings of loneliness, which are risk factors for depression (Holt-Lunstad et al., 2010). Regular physical exercise is another effective preventive measure; it boosts mood through the release of endorphins and supports overall mental health (American Psychological Association, 2011).

Avoiding alcohol and drugs is essential for mental health prevention. Substance abuse is linked to an increased risk of depression, making sobriety a key component of maintaining mental wellness (National Institute on Drug Abuse, 2020). Additionally, adopting a healthy lifestyle that includes balanced nutrition, sufficient sleep, and effective stress management techniques can further prevent the onset of depressive symptoms (Mikkelsen & Papadopoulos, 2020). Early intervention by seeking professional help when needed also plays a crucial role in prevention, providing individuals with strategies to manage stress and emotional challenges before they escalate (Cuijpers et al., 2016). By incorporating these community-based and individual strategies, it is possible to significantly reduce the risk of developing Major Depressive Disorder and promote overall mental well-being.

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References

"Association cortex comprises large-scale, distributed networks across primate species." *Science Direct*, 2021, https://www.sciencedirect.com/topics/neuroscience/association-cortex#:~:text=The%20association%20cortex%20consists%20of,component%20of%20the%20limbic%20system.

"Associations between cortical thickness and general intelligence in children, adolescents and young adults." *NCBI*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3985090/. Accessed 27 August 2024.

"Associations between cortical thickness and general intelligence in children, adolescents and young adults." *NCBI*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3985090/. Accessed 27 August 2024.

Cartreine, James. "More than sad: Depression affects your ability to think." *Harvard Health*, 6 May 2016, https://www.health.harvard.edu/blog/sad-depression-affects-ability-think-201605069551. Accessed 27 August 2024.

"Depression (major depressive disorder) - Symptoms and causes." *Mayo Clinic*, 14 October 2022, https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007. Accessed 27 August 2024.

"Depression - National Institute of Mental Health (NIMH)." *National Institute of Mental Health*, https://www.nimh.nih.gov/health/topics/depression. Accessed 27 August 2024.

"Depression - National Institute of Mental Health (NIMH)." *National Institute of Mental Health*, https://www.nimh.nih.gov/health/topics/depression. Accessed 27 August 2024.

"Depressive disorder (depression)." *World Health Organization (WHO)*, 31 March 2023, https://www.who.int/news-room/fact-sheets/detail/depression. Accessed 27 August 2024.

"How Depression Affects the Brain > News." *Yale Medicine*, 17 June 2021, https://www.yalemedicine.org/news/neurobiology-depression. Accessed 27 August 2024.

"Major Depressive Disorder: Advances in Neuroscience Research and Translational Applications."

PubMed, https://pubmed.ncbi.nlm.nih.gov/33582959/. Accessed 27 August 2024.
"Major Depressive Disorder - StatPearls." *NCBI*, https://www.ncbi.nlm.nih.gov/books/NBK559078/. Accessed 27 August 2024.
"Psychiatry.org - What Is Depression?" *American Psychiatric Association*, https://www.psychiatry.org/patients-families/depression/what-is-depression. Accessed 27 August 2024.
Rakel, RE. "Depression." *PubMed*, https://pubmed.ncbi.nlm.nih.gov/10318745/. Accessed 27 August 2024.
"What Happens To The Brain During Depression - Transformations Center." *Transformations Treatment Center*, https://www.transformationstreatment.center/treatment/what-happens-to-the-brain-during-depression/. Accessed 27 August 2024.
Weist, Mark D., et al. "School-Based Mental Health Services for Elementary-Aged Children: A Meta-Analysis." *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 46, no. 1, 2007, pp. 13-20.
Cuijpers, Pim, et al. "The Effects of Psychotherapies for Major Depression in Adults on Remission, Recovery, and Improvement: A Meta-Analysis." *Journal of Affective Disorders*, vol. 202, 2016, pp. 511-517.
Cuijpers, Pim, et al. "Psychotherapy for Depression in Adults: A Meta-Analysis of Comparative Outcome Studies." *Journal of Consulting and Clinical Psychology*, vol. 78, no. 6, 2010, pp. 920-930. APA PsycNet.
World Health Organization. "Mental Health in the Workplace." *World Health Organization*, 2010. WHO.
Roshanaei-Moghaddam, Behzad, et al. "The Longitudinal Effects of Depression on Physical Activity." *General Hospital Psychiatry*, vol. 33, no. 4, 2011, pp. 365-372. ScienceDirect.
Holt-Lunstad, Julianne, et al. "Social Relationships and Mortality Risk: A Meta-Analytic Review." *PLoS Medicine*, vol. 7, no. 7, 2010, e1000316. PLoS Medicine.
American Psychological Association. "Exercise and Depression." *American Psychological Association*, 2011. APA.
National Institute on Drug Abuse. "Substance Use and Depression." *National Institute on Drug Abuse*, 2020. NIDA.
Mikkelsen, Kristina, and Andreas Papadopoulos. "The Role of Lifestyle Factors in Preventing Depression." *Current Psychiatry Reports*, vol. 22, no. 8, 2020, 65. SpringerLink.
Cuijpers, Pim, et al. "The Effects of Psychotherapies for Major Depression in Adults on Remission, Recovery, and Improvement: A Meta-Analysis." *Journal of Affective Disorders*, vol. 202, 2016, pp. 511-517. ScienceDirect.
Abdijadid, S. "Diagnosis and Management of Major Depressive Disorder." 2023.
Bains, J. "Major Depressive Disorder: Diagnostic Criteria and Clinical Assessment." 2023.
Cohen, J. "Assessment Tools for Depression: The HAM-D and PHQ-9." 2020.
Gordon, R. "Excluding Medical Conditions in Depression Diagnosis." 2021.
Miller, A. "Impact of Major Depressive Disorder on Daily Functioning." 2022.
"Depression (major depressive disorder) - Symptoms and causes." *Mayo Clinic*, 14 October 2022, https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007. Accessed 28 August 2024.
"Biochemistry, Serotonin - StatPearls." *NCBI*, 5 October 2022, https://www.ncbi.nlm.nih.gov/books/NBK560856/. Accessed 29 August 2024.
"Antidepressant effects of ketamine in depressed patients." *PubMed*, https://pubmed.ncbi.nlm.nih.gov/10686270/. Accessed 30 August 2024.
Lee, BC. "Impact of neurological and medical complications on 3-month outcomes in acute ischaemic stroke." *PubMed*, https://pubmed.ncbi.nlm.nih.gov/19049549/. Accessed 30 August 2024.
"Pediatric Antibiotic-refractory Lyme Arthritis: A Multicenter Case-control Study." *PubMed*, https://pubmed.ncbi.nlm.nih.gov/30824653/. Accessed 30 August 2024.