Personalization of Major Depressive Disorder treatment using heterogeneity of depression

Grace Peng

Abstract

There have been trends of increased prevalence of depression disorders worldwide, namely after the COVID-19 pandemic. Major Depressive Disorder (MDD) is the one of the most common mental health conditions in the world, as it affects 3.8% of the global population; however, the condition often generalizes the complex manifestation of symptoms of the disorder, which creates a broad definition and diagnosis of MDD. There are various causes and symptoms that are influenced by genetics, the environment, and development. It is important to create more precise diagnosis in order to better treat depression patients and accommodate their specific needs. SSRI antidepressants are commonly the first prescribed treatment for depression, but they often do not encompass the heterogeneity of depression. By analyzing combinations of biomarkers, risk factors, and treatments of depression, potential directions can be approached to identify paths to make treatment more personalized.

Introduction

Depression is a mood disorder characterized by persistent feelings of sadness, affecting various aspects of people's lives, such as behaviors, thoughts, feelings, and cognitive function. Recently, rates of depression in the U.S. have increased since the start of the COVID-19 pandemic, as rates of anxiety and depression have risen from 24.7% before COVID-19 to 52.5% during COVID-19 (Ettman et al., 2020). Depression is caused by a combination of genetic and environmental factors and can manifest in various ways. Due to its various manifestations and severities, diagnosis is broad and does not encompass the various complexities of depression. Because of this, empirical methods of prescribing medication are limited and impersonalized. When treated, 10%-30% of patients may not respond or give a negative response to typical treatment (Al-Harbi, 2012). If a patient does not respond to antidepressants, the patient may switch medication, which risks issues such as withdrawal or overlapping drug interaction. It is important to note that treatment continues to overlook the complexities of the patient's depression. To further refine diagnoses for depression, we can analyze the similarities and differences of major markers and treatments of depression to further understand its complex mechanisms. The comparisons will further be used to propose effective, personalized treatments for Major Depression Disorder (MDD), one of the most common types of depression. This review will analyze MDD and its different characteristics, such as variations in its risk factors, manifestations, and treatments.

The literature review analyzes the complexities of MDD to improve current clinical measures or treatments to become more personalized and precise. Data collected from various research papers that discuss the causes, manifestations, and treatments of MDD will be used to determine potential methods of treatment and diagnosis.

Risk Factors of Depression

Risk factors are characteristics that are associated with the likelihood of disease. Certain mental processes are associated with the increased likelihood of depression, such as physical health, genetics, environment, or personality traits. The different risk factors that will be analyzed are physical health, genetics, environment, and personality traits that are related to depression.

Physical Health

Physical health and mental health both have a direct and indirect relationship with one another. One longitudinal study examined the effect of past mental health on present physical health. The study uses a mediation framework that demonstrates that mental health has a significant and positive impact on physical health using mediator variables, such as lifestyle choices and social interactions and isolation within the sample (Ohrnberger et al., 2017). The total indirect effects of mental health on physical health are 10%, and physical activity accounts for 77.27% of the indirect impact (Ohrnberger et al., 2017). This relationship is strengthened in older demographics, as the total indirect and total effect of the mediator variables increase with age, implying that age may play a role in the relationship between mental and physical health (Ohrnberger et al., 2017). There are also biological connections between physical and mental health. It is hypothesized that depression and pain share similar neuro-chemical pathways as the neurotransmitters serotonin and norepinephrine modulate both these pathways (Trivedi, 2004; Basbaum & Fields, 1978). For example, the response to painful stimuli is modulated by serotonin and norepinephrine, which are neurotransmitters that are critical targets of depression (Trivedi, 2004), strengthening the connection between physical health and MDD. This connection between MDD and physical ailments, namely pain-related ailments, can elucidate the underlying mechanisms of MDD.

Additionally, due to the varying severities of MDD, understanding the causes of physical ailments in correspondence to MDD can help make treatment more personalized. Physical symptoms can also stem from a physical illness not related to depression, which makes it harder to differentiate if the patient's physical and mental health are correlated (Goodwin, 2006); however, it is still important to recognize that somatic symptoms could be a manifestation of depression and treat it concurrently with emotional symptoms. For example, isolating a mechanism that causes a specific physical ailment and analyzing how that would affect the resulting behaviors that relate to MDD can help create a causation between two factors. This could also allow for more precise clinical treatment, as it could indicate what targets doctors can measure to screen and evaluate for depression. Utilizing certain diagnostic and follow-up evaluation scales that measure both physical and emotional symptoms during treatment could better treat patients and monitor remission.

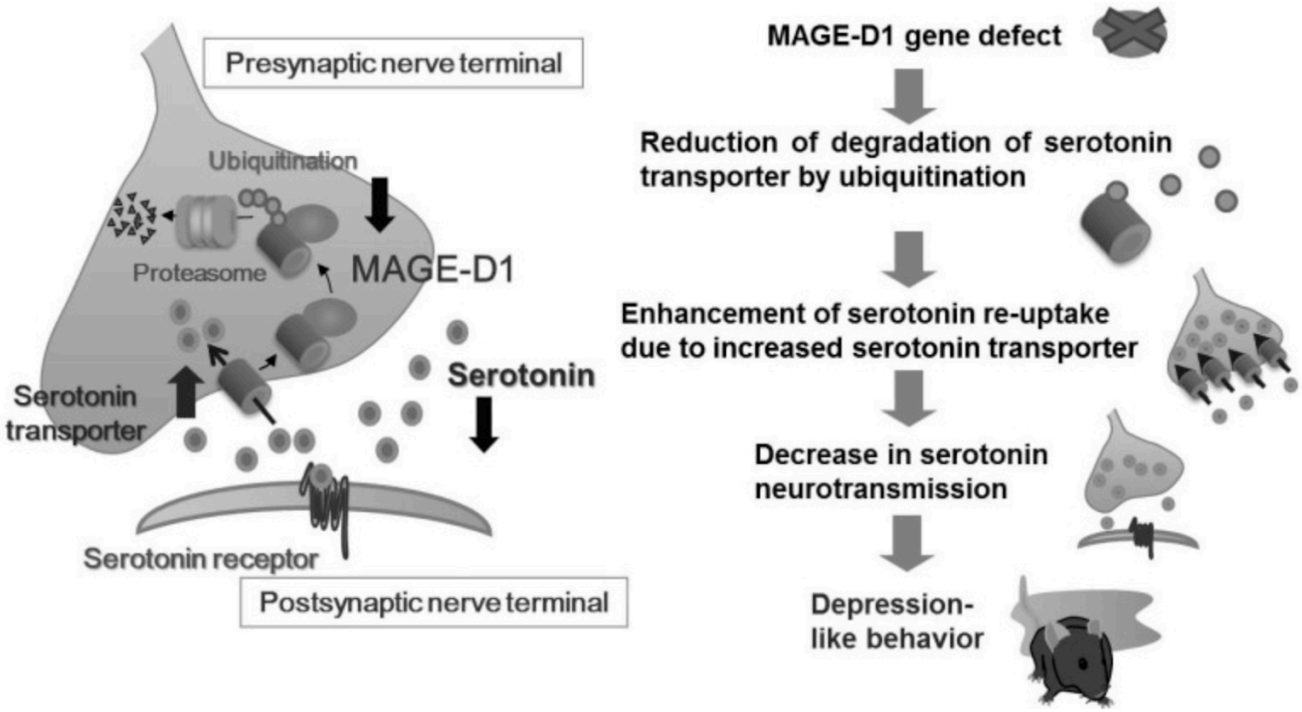
Genetics

There have been previous studies that identify the role of genetics and different variations of depression disorders. Although there is not one specific gene that causes depression, there are several, small candidate genes that have been associated with the manifestation of depression. Studies on genetics in depression have focused on the heredity of depression through linkage studies. In MDD, one of the main biomarkers is the impairment of the serotonin (5-HT) transporter gene, SLC6A4 (5-HTTLPR), as 5-HTTLPR has been useful in predicting antidepressant treatment course, time, and response in patients, which indicates that 5-HTTLPR is a critical target in antidepressants (Lohoff, 2010; Stein et al., 2021). One study shows that the L allele in 5-HTTLPR results in better antidepressant response relative to the S allele (Stein et al., 2021), which could be a marker for personalization of treatment within individuals. Many studies also advocate for other genetic targets. Another potential marker for MDD is Tryptophan Hydroxylase 2 (THP2), which is an enzyme in the brain that regulates the rate of serotonin synthesis (Lohoff, 2010). There are variants of THP2 such as Arg441His that in one study occurred in about 10% of individuals with MDD but was not present in healthy control individuals. The variant caused an 80% loss of function in serotonin production (Lohoff, 2010), which is crucial in depression as a decrease in serotonin is a major indicator of MDD.

Additionally, one study analyzed the gene defect of the melanoma-associated antigen D1 (MAGE-D1) gene in mice. An impairment in MAGE-D1 causes a decrease in serotonin, as serotonin transporters are not ubiquitinated and transporters remain undegraded, causing more serotonin to be reuptaken and creates depressive-like behaviors in mice (Fig. 1) (Nabeshima & Kim, 2013). As a result, the study indicates that researchers could look into using ubiquitinated serotonin as a marker for depression (Nabeshima & Kim, 2013). The different candidate genes are not seen throughout every individual with MDD, which implies the different genetic factors of depression; however, these differences can be utilized to create different targets for treatment. Genetics only cause a predisposition to mental disorders, but do not imply that the subject will develop MDD; they can, however, weaken resistance to negative environmental factors that can induce depression (Nabeshima & Kim, 2013).

Figure 1.

Effect of MAGE-D1 Gene Defect in Mice



Note. The figure illustrates a diagram of the role of the MAGE-D1 gene in neurotransmission. The image depicts how the impairment in the MAGE-D1 gene results in decreased ubiquitinated serotonin transporters, increasing serotonin reuptake and decreases the time the serotonin remains in the synaptic cleft. From “Involvement of Genetic and Environmental Factors in the Onset of Depression” by T. Nabeshima and H. Kim, 2013, *Experimental neurobiology*, *22*(4), p. 238. Copyright 2013 by *Experimental Neurobiology*.

Environment

The developmental stage can increase risk of developing depression later on in life. While depression can manifest throughout someone’s life, two periods of development mainly lead to the onset of depression: the embryonic or perinatal stage and puberty (Nabeshima & Kim, 2013). During the embryonic stage, if the patient experiences certain environmental stressors—such as undernourished birthing, winter birth, growth in a large city, obstetric complications, birth/growth in a large city, or relationships with family members—or has specific

genetic mutations such as the aforementioned candidate genes, the subject is at risk for the onset of depression (Nabeshima & Kim, 2013). If additional environmental stressors are present during puberty, they are likely to develop affective disorders (Nabeshima & Kim, 2013). Additionally, without neuroplasticity in certain regions, the brain is not able to adapt well to certain life events and stressors, leading to the development of depression. For example, a longitudinal study observed the lives of 10,045 participants and the influence of drastic life events. They found that the combination of life events—such as personal problems, relationship problems, and problems with the law—are large risks to the onset of depression (Stegenga et al., 2012). They also found that women ages 40 to 49 are more likely to be affected than the other age and gender groups, which further shows the influence of the interaction of environmental and biological factors on the onset of depression. Environmental factors play a key role in the onset of depression, which demonstrates that promoting a favorable, safe environment can help reduce the risk of depression. It is also important to take note that various factors, including age and sex, can alter how people respond to their environment, which indicates how different treatments are needed to better fit people's needs.

Personality Traits

Certain models of personality are used to characterize depression, such as the Five-Factor Model (FFM). There are multiple proposed ways that personality correlates to depression and they are categorized into two groups. One group states that personality and depression are caused by similar factors, but do not cause the other. The other group states that personality and depression influence the other. These models can further indicate personality as a factor for more precise diagnosis (Klein et al., 2011). The FFM, which includes conscientiousness, agreeableness, neuroticism, openness, and extraversion, represents the dimensions that characterize individuals' personalities. Depression is often associated with higher levels of neuroticism and lower levels of conscientiousness, extraversion, and agreeableness (Lester, 2021). High levels of neuroticism reflect emotional instability, which often leans towards symptoms of depression and anxiety. According to the FFM, either the traits cause people to be more susceptible to depression or it affects how people react to big life events and their environment, which can influence the onset of depression (Lester, 2021). Differences in personality contribute to the heterogeneity of depressive disorders due to various developmental pathways converging. This could help inform more precise depression diagnosis and create more subtypes of depression.

Biomarkers of Depression

A biological marker (biomarker) provides a measurement of the processes that occur in the body and can serve as an indicator of the state of a patient. There are different types of brain biomarkers—structural and functional—that manifest in different types of depression.

Structural.

Structural biomarkers consist of characteristics such as alterations in gray matter volume, atrophy in regions of the brain, etc., and can be identified using neuroimaging techniques, such as Magnetic Resonance Imaging (MRI). The structural biomarkers are important in identifying surface-level targets that may be useful for improving diagnosis and making treatment more precise. Many studies highlight the patterns of structural alterations among different MDD patients in comparison to healthy controls. Using MRI scans, researchers were able to identify patterns of volume reduction or atrophy across various MDD patients compared to healthy individuals. A study highlights that many MDD patients have major structural differences in the frontal lobe, hippocampus, temporal lobe, thalamus, striatum, and amygdala (Zhang et al.,

2018). These structural differences could potentially be used as measures for clinical diagnosis and treatment, as clinical diagnosis more often relies on the emotions and functionality of patients (Rădulescu et al., 2021). Studies highlight the importance of the structural alterations in the limbic and cortical regions of the brain. The limbic region, namely the hippocampus and the amygdala, is responsible for the regulation of emotion, mood, and memory.

Neural plasticity is the ability of the brain to change and adapt to stimuli so that the brain can reorganize itself, strengthening and weakening synaptic transmission, formation, regeneration, etc. (Rădulescu, 2021). Because of these adaptations, functions can change which ultimately can cause behaviors to alter. Differences in age and sex can influence the levels of neuroplasticity between people. For example, during adolescence, the brain is more susceptible to periods of change and growth because of instances such as puberty, where the body tries to regulate its functions. This allows for periods of learning and growth, as neuroplasticity allows people to learn from their experiences; however, neuroplasticity can be changed or inhibited in limbic regions of the brain—associated with negative rumination and fear learning—in depression (Rădulescu et al., 2021). This increases vulnerability to the development of mental disorders, such as anxiety or depression.

In MDD, the hippocampus—associated with memory and complex cognitive processes, such as negative emotion and disruption and cognitive processing (Zhang et al., 2018)—is part of the limbic region. The hippocampus plasticity is often reduced during depression (Table 1). The inhibition of hippocampus plasticity is caused by higher levels of plasmatic cortisol and glucocorticoids (Rădulescu et al., 2021; Liu et al., 2017) which makes plasmatic cortisol and glucocorticoids a potential clinical marker to measure for the risk of developing depression.often reduces in gray and white matter volume (Rădulescu et al., 2021; Zhang et al., 2018; Liu et al., 2017). Additionally, the hippocampus experiences a reduction in gray and white matter due to atrophy of neurons and increased glucocorticoid levels, which is caused by genetics or outside factors such as stress. However, the volume of the hippocampus varies among patients with MDD and correlates to recovery time, as one study demonstrates that relatively greater hippocampus gray matter volume in MDD patients results in quicker recovery time (Liu et al., 2017). Volume, however, does not indicate the severity of depression (Liu et al., 2017). On the other hand, the amygdala experiences an increase in gray and white matter. This correlates to the function of the amygdala—which is responsible for memory encoding and fear conditioning—where hyperactivity can lead to depressive-like behavior. The amygdala volume, unlike the hippocampus, varies with the severity of depression, which can be used as a marker for identifying the severity of depression in clinical settings.

Table 1

Changes of Neural Plasticity in Hippocampus

Brain region	Changes of neural plasticity	Mechanisms
Hippocampus	Synaptic plasticity	(1) Impairment of LTP in CA3 (2) Facilitation of LTD and tLTD in CA1 (3) Downregulation of synaptic proteins and growth factors

	Volumetric changes	(1) Disruption and atrophy of neurons and glia (2) Neurodegenerative reaction to high levels of glucocorticoid
	Neurogenesis	(1) Hindered by high levels of glucocorticoids and enhanced by adrenalectomy (2) Additive effects in mice, while reduced in humans (3) Additive function in the circuitry
	Apoptosis	(1) Depression promotes apoptosis in the hippocampus (2) The effects caused by chronic depression last longer than those of acute depression
Amygdala	Synaptic plasticity	(1) Increased expression of BDNF (2) Disrupted glutamate signaling at the NMDA receptor (3) Neonatal glucocorticoid treatment enhances LTP
	Volumetric changes	(1) Larger gray matter volume in the bilateral amygdala
	Functional connectivity	(1) Decreased bilateral amygdala-right insular cortex connectivity (2) In the left amygdala, the functional connectivity decreased in positive network and increased in negative network (3) Amygdala-associated brain circuits may change

with depression severity
(4) Prenatal maternal depression increases functional connectivity in infants

Note: Data illustrates the various changes in neural plasticity (i.e. synaptic plasticity, volumetric changes, neurogenesis, and apoptosis) in the hippocampus in depression. The table only includes the hippocampus and amygdala sections of the original table as the other contents are not relevant. Reprinted from "The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex" by W. Liu et al., 2017, *Neural Plasticity, 2017*, 6871089. Copyright 2017 by Wei Liu et al.

Functional

Functional biomarkers can be identified using different neuroimaging techniques, such as Functional Magnetic Resonance Imaging (fMRI). Some functional biomarkers include alterations in the circuitry of the brain, as communication and activity between different regions of the brain are altered. For example, the prefrontal-subcortical circuit—which includes the striatum, thalamus, and prefrontal cortex—is often impaired in MDD patients (Zhang et al., 2018). Because of impairments in the pathway, the thalamus, which is responsible for emotional regulation, is suppressed. This could connect to the structural impairment of the thalamus and its reduction in volume. By identifying which specific regions are altered and why, researchers can potentially target a certain pathway to analyze. Analyzing how this certain pathway interacts with other pathways in the brain could open up more information about the mechanisms behind MDD.

Additionally, proteins are important in brain function, as they are essential in the functionality and structure of neurons. Certain studies identify select proteins that could play a key role in depression. Brain-derived neurotrophic factor (BDNF), is a protein that is reduced in the hippocampus and is associated with depressed mood and traits (Lohoff, 2010). Additionally, in many effective antidepressants, BDNF levels increase, which implies that BDNF could be a potential target for treatment (Nabeshima & Kim, 2013). By further analyzing the roles of proteins in depression, they can be used as clinical measures to diagnose and treat depression.

Analysis of MDD Treatments

Conventional treatments, such as pharmaceutical medications, are a way depression is commonly treated. Antidepressants are prescribed to help regulate the brain and neurotransmission levels. Depression is often linked to a serotonin deficiency, as serotonin regulates happiness and optimism. One common class of antidepressants used is Selective Serotonin Reuptake Inhibitors (SSRIs), which are commonly first prescribed to those taking antidepressants. Serotonin deficiency can be caused by lower levels of neurotransmitters available or nerves reuptaking serotonin too quickly. At a cellular level, SSRIs prevent the serotonin transporter (SERT) from taking up serotonin to increase the amount of serotonin in the synapse (Chu & Wadhwa, 2023), which allows higher transmission of serotonin.

Around 10%-30% of patients may not respond to different kinds of SSRI treatments or give a negative response (Al-Harbi, 2012), which requires them to use atypical treatment. To further understand why patients may not respond to treatment, studies must further analyze what factors are linked to antidepressant response. One common method used in the analysis of Treatment-Resistant Depression (TRD), a subset of MDD, takes into account environmental,

developmental, and genetic considerations to give further insight into why some patients do not respond to treatment. One study compares antidepressant treatment within different animal models to humans to find implications within humans. By genetically modifying mice, scientists were able to remove the 5-HT1A receptor, which reduced the effectiveness of the SSRI antidepressant (Akil et al., 2018), which highlights the 5-HT1A receptor as an important factor in depression treatment. By analyzing the 5-HT1A receptor in those who are not responsive to SSRI treatment, researchers can confirm impairment in 5-HT1A as an explanation for TRD. Another approach taken is to identify patterns in the demographic of those who do and do not respond to treatment. The L allele in the serotonin transporter gene, 5-HTTLPR, is associated with better antidepressant response; the response is seen to be further improved in demographics with either European ancestry or in females with MDD (Stein et al., 2021). Researchers can look into potential differences in genetic biomarkers in these demographics compared to other demographics to see if there is a significant difference. To better antidepressant treatment to possibly treat TRD, researchers can further analyze the differences and similarities between MDD and TRD pathways.

Complementary treatments—such as non-pharmacological treatments—can be used in conjunction with conventional medicine to further improve its effectiveness. One common complementary treatment for depression is cognitive behavioral therapy (CBT), which is an intervention that aims to alter the thoughts and behaviors of MDD patients. Additionally, across multiple studies, exercise was shown to positively affect mental health (Ohrnberger et al., 2017), and it can also prevent changes in neural plasticity during depression (Liu et al., 2017). Other methods, such as electroconvulsive therapy can be used to increase neural plasticity and reduce the effects of depression (Liu et al., 2017). Some studies bring up some uncommon therapies, like electroacupuncture or neurofeedback to treat depression. These potential treatments can be further explored to help enhance and personalize treatment for MDD patients in the future.

Discussion

While researchers continue to explore the mechanisms of depression, it is important to continue to consider how different pathways interact to manifest different biological, somatic, and psychological symptoms. These various risk factors and biomarkers often influence each other to create a variety of manifestations within a patient. To identify the specific mechanisms that tie into the multi-dimensional causes of depression, it is important to analyze the causes and importance of various risk factors and biomarkers to elucidate the underlying mechanisms within MDD. One potential pathway that could be further explored is the effect of THP2 on depression, as it is seen in MDD patients but not in healthy controls. It would also be beneficial to further analyze the effect of physical health and mental health to better understand how to differentiate between a cause-and-effect relationship or separate illnesses during diagnosis and treatment. To go further in depth, researchers can compare and contrast different types of depression (MDD, TRD, seasonal, persistent, etc.) and see how disparities between certain factors can lead to certain symptom manifestations. After identifying specific differences between the specified subtypes, researchers can continue to analyze the complexities of risk factors and biomarkers within depression to create new subtypes of MDD.

With the different risk markers and biomarkers, doctors can create more precise diagnosis for MDD. Across multiple studies, researchers mentioned the importance of alterations in gray and white matter volume in the limbic regions of the brain—the hippocampus and amygdala—in MDD patients to healthy controls. The differences in volume could be

measured as a biomarker for depression, as these impairments lead to depression or depressive-like symptoms. Personality can also be used as a marker for depression, as the FFM demonstrates patterns of higher neuroticism and lower extraversion, agreeableness, and conscientiousness leading to depression-like symptoms. Some genetic factors—like identifying impairments of 5-HTTLPR or monitoring levels of ubiquitinated serotonin transporters—could be identified as risk markers to take early action to possibly prevent the onset of depression. Studies demonstrate not solely genetic factors, but the combination of genetics and environment that leads to the onset of MDD, showing the great influence of the environment on MDD. If genetic risk markers are identified, one possible intervention to lessen the risk of MDD is to facilitate a positive environment and promote more positive lifestyle choices and social capital.

Various paths can be used to try and better current depression treatment. Treatment should take into account that somatic symptoms could be manifestations of MDD and be treated and monitored in conjunction with the emotional symptoms; however, there are other cases where somatic symptoms and emotional symptoms are completely unrelated. Further research can explore the similarities and differences in the pathways between physical symptoms caused by and separate from depression to better understand the relationship between pain and MDD. This would allow for more understanding to help treat MDD. Follow-up screenings using tests, such as QIDS, can be used to monitor remission and identify the effectiveness of treatment. Alongside the major neurotransmitters in depression—serotonin and norepinephrine—other potential targets can be used for antidepressant treatment, such as glucocorticoid or BDNF. Increased levels of glucocorticoid in the hippocampus lead to inhibited hippocampal plasticity, which means that glucocorticoid levels could potentially be regulated. Additionally, decreased BDNF levels often produce depressive traits, and BDNF levels increase in effective antidepressants; however, there are conflicting studies about using BDNF as a target for treatment, which implies that this target can be further explored. It is important to recognize that antidepressants and complementary treatments can be used in conjunction to enhance the effectiveness and personalization of treatment. Across multiple studies, exercise has been shown to boost mental health and even prevent changes in neural plasticity. Other studies have targeted electroconvulsive therapy, electroacupuncture, and neurofeedback as potential interventions.

Conclusion

It is crucial to continue to work towards developing effective, precise treatment for MDD and its subtypes to benefit the community, as depression symptoms affect both the individual and society, and if left untreated, can lead to increased risk of suicide, decreased production in the workforce, and hindrance of the relationships within a community. Depression is prevalent around the world, as it currently affects around 3.8% of the population around the world (WHO, 2023). MDD is a complex disorder caused by the interaction of many environmental, developmental, and genetic factors throughout life, which causes various manifestations among individuals. While there are some general patterns in behavior, the broad definition of MDD is not precise enough to fully cover the different psychological, biological, and somatic symptoms that stem from various intertwining pathways. It is important to understand that these complexities of depression are important to enhance the treatment and diagnosis of depression and that much research is still needed to further understand these complexities. When analyzing depression, researchers must acknowledge that the different factors influence each other and are part of a larger, complex system.

References

[1] Akil, H., Gordon, J., Hen, R., Javitch, J., Mayberg, H., McEwen, B., Meaney, M. J., & Nestler, E. J. (2018). Treatment resistant depression: A multi-scale, systems biology approach. *Neuroscience and biobehavioral reviews, 84*, 272–288. https://doi.org/10.1016/j.neubiorev.2017.08.019

[2] Al-Harbi, K. S. (2012). Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient preference and adherence, 6*, 369–388. https://doi.org/10.2147/PPA.S29716

[3] Basbaum, A. I., & Fields, H. L. (1978). Endogenous pain control mechanisms: review and hypothesis [Abstract]. *Annals of neurology, 4*(5), 451–462. https://doi.org/10.1002/ana.410040511

[4] Chu, A., & Wadhwa, R. (2023). Selective serotonin reuptake inhibitors. *StatPearls.* https://www.ncbi.nlm.nih.gov/books/NBK554406/

[5] Ettman, C. K., Abdalla, S. M., Cohen, G. H., Sampson, L., Vivier, P. M., & Galea, S. (2020). Prevalence of depression symptoms in US adults before and during the COVID-19 Pandemic. *JAMA network open, 3*(9), e2019686.

[6] Goodwin, G. M. (2006). Depression and associated physical diseases and symptoms. *Dialogues in clinical neuroscience, 8*(2), 259–265. https://doi.org/10.31887/DCNS.2006.8.2/mgoodwin

[7] Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Experimental and clinical psychopharmacology, 23*(1), 1–21. https://doi.org/10.1037/a0038550

[8] Höller, Y., Urbschat, M. M., Kristófersson, G. K., & Ólafsson, R. P. (2022). Predictability of seasonal mood fluctuations based on self-report questionnaires and EEG biomarkers in a non-clinical sample. *Frontiers in psychiatry, 13*, 870079. https://doi.org/10.3389/fpsyt.2022.870079

[9] Klein, D. N., Kotov, R., & Bufferd, S. J. (2011). Personality and depression: explanatory models and review of the evidence. *Annual review of clinical psychology, 7*, 269–295. https://doi.org/10.1146/annurev-clinpsy-032210-104540

[10] Lester, D. (2021). Depression, Suicidal Ideation and the Big Five Personality Traits. *Austin J Psychiatry Behav Sci, 7*(1), 1077. https://austinpublishinggroup.com/psychiatry-behavioral-sciences/fulltext/ajpbs-v7-id1077.php

[11] Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., & Cui, R. (2017). The role of neural plasticity in depression: From hippocampus to prefrontal cortex. *Neural plasticity, 2017*, 6871089. https://doi.org/10.1155/2017/6871089

[12] Lohoff, F. W. (2010). Overview of the genetics in major depressive disorder. *Current psychiatry reports, 12*(6), 539–546. https://doi.org/10.1007/s11920-010-0150-6

[13] Nabeshima, T., & Kim, H. (2013). Involvement of genetic and environmental factors in the onset of depression. *Experimental neurobiology, 22*(4), 235–243. https://doi.org/10.5607/en.2013.22.4.235

[14] Norkeviciene, A., Gocentiene, R., Sestokaite, A., Sabaliauskaite, R., Dabkeviciene, D., Jarmalaite, S., & Bulotiene, G. (2022). A systematic review of candidate genes for major depression. *Medicina (Kaunas, Lithuania), 58*(2), 285. https://doi.org/10.3390/medicina58020285

[15] Ohrnberger, J., Fichera, E., & Sutton, M. (2017). The relationship between physical and mental health: A mediation analysis. *Social Science & Medicine, 195*, 42–49. https://doi.org/10.1016/j.socscimed.2017.11.008
[16] Rădulescu, I., Drăgoi, A. M., Trifu, S. C., & Cristea, M. B. (2021). Neuroplasticity and depression: Rewiring the brain's networks through pharmacological therapy (Review). *Experimental and therapeutic medicine, 22*(4), 1131. https://doi.org/10.3892/etm.2021.10565
[17] Shadrina, M., Bondarenko, E. A., & Slominsky, P. A. (2018). Genetic factors in major depression disease. *Frontiers in psychiatry, 9*, 334. https://doi.org/10.3389/fpsyt.2018.00334
[18] Stein, K., Maruf, A. A., Müller, D. J., Bishop, J. R., & Bousman, C. A. (2021). Serotonin transporter genetic variation and antidepressant response and tolerability: A systematic review and meta-analysis. *Journal of personalized medicine, 11*(12), 1334. https://doi.org/10.3390/jpm11121334
[19] Stegenga, B. T., Nazareth, I., Grobbee, D. E., Torres-González, F., Svab, I., Maaroos, H. I., Xavier, M., Saldivia, S., Bottomley, C., King, M., & Geerlings, M. I. (2012). Recent life events pose greatest risk for onset of major depressive disorder during mid-life. *Journal of affective disorders, 136*(3), 505–513. https://doi.org/10.1016/j.jad.2011.10.041
[20] Trivedi, M. H. (2004). The link between depression and physical symptoms. *Primary care companion to the Journal of clinical psychiatry, 6*(Suppl 1), 12–16.
[21] World Health Organization. (2022). COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide. https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide
[22] World Health Organization. (2023). Depressive disorder (depression). https://www.who.int/news-room/fact-sheets/detail/depression
[23] Zhang, F. F., Peng, W., Sweeney, J. A., Jia, Z. Y., & Gong, Q. Y. (2018). Brain structure alterations in depression: Psychoradiological evidence. *CNS neuroscience & therapeutics, 24*(11), 994–1003. https://doi.org/10.1111/cns.12835